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RELATIONSHIP BETWEEN ANATOMIC CHANGES IN KNEE JOINT WITH ADVANCING AGE AND DEGENERATIVE ARTHRITIS

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The acquirement of knowledge concerning arthritis has been delayed by a lack of detailed information regarding the changes which may be encountered with advancing age. Such information is highly desirable in order to assist in defining the limits of normal for a given age period. It is of further importance from the point of view of the ultimate changes that may occur in a joint which has been the site of an injury resulting from invasion by infective agents, and, finally, it provides knowledge regarding the early stages of disorders of the joints. For these reasons we have made a systematic study of 100 knee joints removed at consecutive necropsies, and in this article we detail the gross anatomic findings and discuss their significance.

MATERIAL AND METHODS

One hundred knee joints were removed from 77 cadavers. The cases were not selected on the basis of previous clinical diagnosis or the presence of symptoms in the joints. The only cases excluded from the group were those in which there was definite infection of the joints with various organisms, as determined by bacteriologic examination of the fluid found in the joints at necropsy. A study of these joints will be presented separately. Whenever possible, the whole knee joint was removed together with its capsule and a portion of the femur and tibia. When this was not feasible, the joint was opened by cutting across the inferior patellar ligament and reflecting the patella. The articular surfaces of the patella, femur and tibia were then removed in such a way that the surfaces could be reconstructed and studied. The gross changes were noted, and material was taken for histologic section.

In this paper the term degenerative arthritis is used synonymously with hypertrophic arthritis and osteo-arthritis.

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ANATOMIC CONSIDERATIONS

It is not our purpose to comment in detail on the anatomy of the knee joint. It is necessary to know some of the salient facts before one can clearly understand the changes which were found. The relevant facts are recalled herewith.

The articulations of the knee joint are divided into the following groups: (1) the articulation of the patella with the femur, and (2) the articulations of the two condyles of the femur with the corresponding meniscus and condyle of the tibia.

The articulation of the patella with the femur is partly a gliding one, but as the articular surfaces are not mutually adapted to each other, the movement is not a simple gliding one. This fact will become obvious when the various movements of the knee joint are analyzed in detail.

For the purpose of describing the movements of the patella and its articular surface, it may be divided roughly into seven facets: the upper, middle and lower horizontal pairs and a median perpendicular facet.

The surface of the femur which articulates with the patella is named the patellar or anterior surface. It presents a median groove which extends downward to the intercondyloid fossa and two convexities, the lateral one of which is broader and more prominent and extends farther upward than the medial. In the extended position of the leg, when the quadriceps femoris is relaxed, the patella lies loosely on the front of the lower end of the femur. When the knee is forcibly flexed the median perpendicular facet is in contact with the semilunar surface of the lateral part of the medial condyle of the femur; this semilunar surface is a backward prolongation of the medial part of the patellar surface of the femur. As the leg is carried from the flexed to the extended position, first the upper, then the middle and finally the lowest pair of horizontal facets is successively brought into contact with the patellar surface of the femur. In the process of walking, in which the leg is alternately extended and semiflexed, the part of the patella which is brought into contact with the femur is the median pair of horizontal facets. The importance of this will be stressed presently.

The lower and posterior parts of the articular surface of the femur constitute the tibial surfaces for articulation with the corresponding condyles of the tibia and menisci. These surfaces are separated from one another by the intercondyloid fossa and from the patellar surface by faint grooves which extend obliquely across the two condyles. The lateral groove is better marked; it runs lateralward to form a triangular depression.

The articular surface of the tibia consists of two facets, the central portions of which articulate with the condyles of the femur, while their peripheral portions support the menisci of the knee joint which here

intervene between the two bones. Between the two facets is the intercondyloid eminence, surmounted on either side by a prominent tubercle, onto the sides of which the articular facets are prolonged. The lateral condyle is usually somewhat smaller than the medial and is nearly circular.

In the position of extension, when the subject is standing erect, the weight of the trunk is transmitted from the head of the femur in a vertical line which passes through the external condyle of the femur and tibia.

When full extension of the leg is reached and maintained the lateral part of the groove of the lateral condyle of the femur is pressed against the anterior part of the corresponding meniscus, while the medial part of the groove rests on the articular margin in front of the lateral process of the tibial intercondyloid eminence. Into the groove on the medial condyle is fitted the anterior part of the medial meniscus, while the anterior crucial ligament and the articular margin in front of the medial process of the intercondyloid eminence are received into the forepart of the intercondyloid fossa of the femur.

In full flexion, the posterior parts of the femoral condyles rest on the corresponding parts of the meniscotibial surfaces, and the semilunar area of the median condyle articulates with the median vertical facet of the patella. As the limb moves from flexion to extension the posterior two thirds of the tibial articular surfaces of the two femoral condyles gradually shift forward and the patella moves upward in the manner previously described.

In walking, greater weight is placed on the lateral condyle of the tibia than on the median, and the inferior surface of the femoral condyles articulates with the corresponding articular surfaces of the tibial condyles. With these facts borne in mind, the results of our investigation are detailed.

Sex and Age.—Of the 100 joints, 67 were obtained from males and 33 from females. From tables 1, 2 and 3, it is seen that the changes observed were as common in women as in men. No qualitative difference in the type of anatomic alterations in the joints was observed. For these reasons the gross changes in the two sexes are considered together.

The age distribution of the patients whose joints were studied is given in figure 1. In figure 2 the total percentage of joints showing changes at various age periods is shown, and it is obvious that the anatomic deviations from normal increase with advancing age.

Occupation.—As degenerative arthritis is sometimes explained on the basis of a person's occupation or at least is aggravated by certain occupations that require the excessive use of the joints, an analysis was made of the patients' occupations. They are summarized in table 4.

TABLE 1.—*Site of Observed Anatomic Changes in the Knee Joints in Various Decades of Life (Males)*

Age, Years	Number of Joints	Patella	Femur			Tibia	
			Interpatellar Groove	Median Condyle	Lateral Condyle	Median Condyle	Lateral Condyle
0- 9	2	0	0	0	0	0	0
10-19	0	0	0	0	0	0	0
20-29	0	0	0	0	0	0	0
30-39	4	1	1	0	0	2	2
40-49	8	4	3	1	0	2	4
50-59	14	13	9	7	4	9	9
60-69	17	16	13	7	3	10	11
70-79	16	15	15	11	11	10	12
80+	6	5	3	2	2	4	4
Total	67	54	44	28	20	37	42

TABLE 2.—*Site of Observed Anatomic Changes in the Knee Joints in Various Decades of Life (Females)*

Age, Years	Number of Joints	Patella	Femur			Tibia	
			Interpatellar Groove	Median Condyle	Lateral Condyle	Median Condyle	Lateral Condyle
0- 9	1	0	0	0	0	0	0
10-19	2	0	0	0	0	0	0
20-29	1	0	0	0	0	0	0
30-39	2	1	1	0	0	1	1
40-49	1	0	0	0	1	0	0
50-59	6	5	4	4	4	4	6
60-69	11	12	10	6	6	7	8
70-79	3	4	3	2	2	2	2
80+	6	5	3	3	3	4	5
Total	33	27	21	15	16	18	22

TABLE 3.—*Total Changes in Both Sexes, Showing Site of Anatomic Alterations*

Age, Years	Number of Cases	Number of Joints	Patella	Femur			Tibia	
				Median Condyle	Lateral Condyle	Interpatellar Groove	Median Condyle	Lateral Condyle
0- 9	3	3	0	0	0	0	0	0
10-19	2	2	0	0	0	0	0	0
20-29	1	1	0	0	0	0	0	0
30-39	5	6	2	0	0	2	3	3
40-49	7	9	4	1	1	3	2	4
50-59	14	20	18	11	8	13	13	15
60-69	23	28	28	13	9	23	17	19
70-79	15	19	19	13	13	18	12	14
80+	7	12	10	5	5	6	8	9
Total	77	100	81	43	36	65	55	64

TABLE 4.—*Occupations of the Patients*

Laborers	30
Housewives	21
Artisans	17
Cooks and waiters	4
Workers in offices	4
Professional worker	1

In a further analysis of the extent of anatomic change and occupation we were unable to determine any relationship between the extent of the damage and the occupation, but data concerning the actual details of the patients' life-long daily careers were not available.

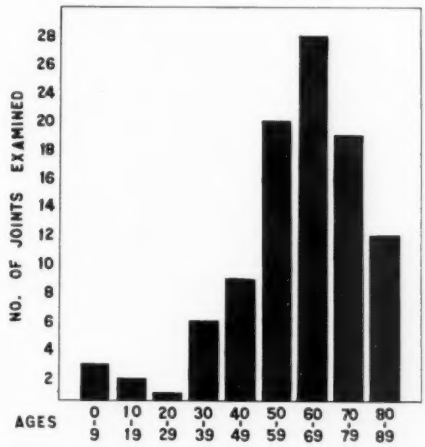

Fig. 1.—Age distribution of the 77 patients whose knee joints were examined.

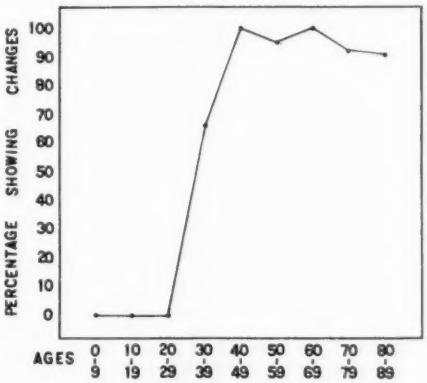

Fig. 2.—The percentage of cases showing anatomic changes in the knee joints at different age periods.

Cause of Death.—The diseases from which the patients died are listed in table 5. From this table it is seen that no one disease or group of diseases could be held responsible for the changes observed.

Relationship Between Anatomic Lesions and Symptoms Referable to the Joints.—There were no symptoms recorded in the clinical his-

tories of 66 patients, and pain and stiffness were present in only 11 of the 77 patients. When symptoms referable to the joints are present in a patient with anatomic changes in the joints such as we have observed, it is necessary to look for other factors in order to explain the symptoms. From our observations it is manifest that pathologic changes in the joints were present with equal frequency in both sexes, that they increased in frequency with advancing age and that neither the cause of death nor the occupation of the patients was of significance in accounting for the condition of the joints.

Changes in the Patella.—The articular surface of the patella showed distinctive alterations in 81 of the joints examined. The sites of the changes are recorded in table 6. In most cases the median surface

TABLE 5.—*Diseases Responsible for Death*

Lobar pneumonia and bronchopneumonia	20
Arteriosclerotic heart disease	15
Cancer (miscellaneous)	10
Cerebral hemorrhage	6
Tuberculosis	8
Peritonitis (generalized)	3
Pyelonephritis	5
Rheumatic heart disease	4
Syphilitic aortitis with aneurysm or aortic insufficiency	2
Pernicious anemia	1
Aplastic anemia	1
Osteogenic sarcoma	1
Bacterial endocarditis	1
Total	77

TABLE 6.—*Position of Changes in the Patella*

	Median Surface	Lateral Surface
Superior horizontal facets	14	17
Median horizontal facets	75	61
Inferior horizontal facets	22	19

showed alterations more often than the lateral surface, and the median horizontal facets were involved more often than the other two pairs. This is significant because this is the part of the patella which comes in contact with the patellar surface of the femur most frequently in such movements as walking. The inferior pair were changed more often than the superior, and again this pair of facets comes in contact with the femur more often than the superior pair.

The character and degree of the erosions varied tremendously in different cases. Figure 3 illustrates the kind of alterations observed. It is seen that there may be simple fibrillation of the cartilage, with irregularity of the surface or loss of varying amounts of cartilaginous substance so that in some cases the underlying bone is exposed. In the places where the bone was exposed it was usually very dense and, in some cases, shiny, giving an appearance of a highly polished surface, the so-called eburnated bone.

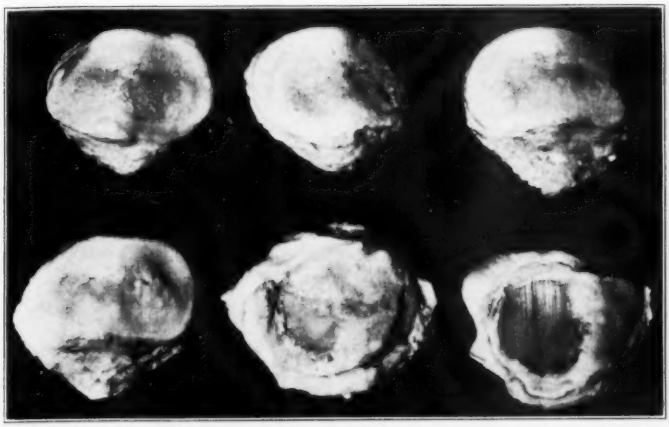

Fig. 3.—Photographs of the articular surface of the patella, showing the type of anatomic alterations observed. Various degrees of changes are present. In some cases there is only fibrillation of the cartilage; in others the underlying bone is exposed.

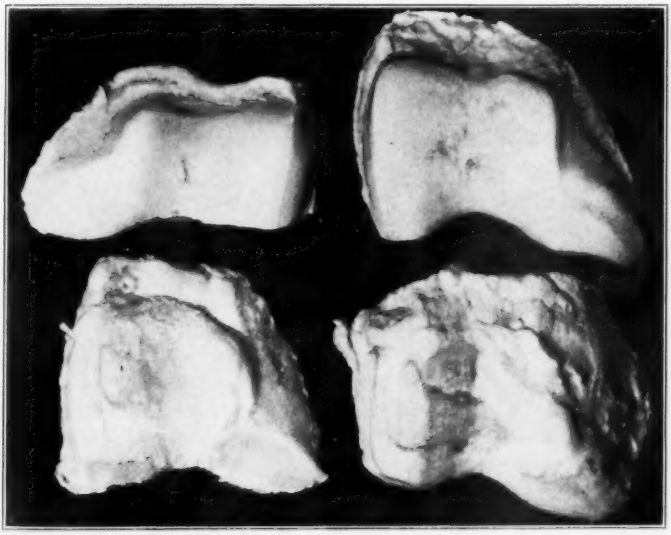

Fig. 4.—Photographs of the patellar groove of the femur, illustrating the type of lesion observed. The lesion is progressively more extensive in the specimens shown.

Femur.—For purposes of discussion we have divided the articular surfaces of the femur into the patellar groove, the anterior and posterior articular surfaces of the condyles and the median surface of the median condyle.

Patellar (Intercondyloid) Groove: This area of the femur was altered in 65 cases. In every case the erosion was situated at the point where the patella comes in contact with the femur. In most instances the eroded area was in the center of the groove; in others, it was at the right or left, depending on the size, shape and position of the patella when in contact with the femur. Figure 4 illustrates the site and type

Fig. 5.—Photograph of the articular surface of the patella and the patellar groove of the femur, showing the erosions on the articulating surfaces.

of the erosions which were seen. In every case in which changes were observed in the interpatellar groove there was an irregular or eroded area on the patella at the point where it came in contact with the femur. This is illustrated in figure 5. The recognition of this fact is highly important in interpreting the findings.

Anterior Articular Surface of Femoral Condyles: It is to be recalled that the medial and lateral anterior articular surfaces of the femoral condyles come in contact with the tibial condyles and the corresponding menisci. The median condyle showed erosions in 46 joints and the lateral condyle in 36. These areas were most conspicuous at the point where the condyles were in contact with the central portion

of the tibia which was uncovered by the lateral or median meniscus. An example of these erosions is shown in figure 6.

Aside from the lesions on the anterior articular surface, erosions were observed on the median surface of the median condyle in 9 cases. They are illustrated in figure 7 and require special comment. It has already been pointed out that when the leg is in full extension the medial process of the intercondyloid eminence of the tibia and the anterior cruciate ligament are received into the forepart of the intercondyloid fossa of the femur. When a large number of these joints are examined, it becomes apparent that in some cases this eminence is high and promi-

Fig. 6.—Photograph of the inferior articular surfaces of the femur and the corresponding articular surfaces of the tibia, showing the type and position of the irregularities and erosions.

nent and is in direct contact with the lateral surface of the median condyle, especially during flexion and extension. In every case in which we observed an erosion of the femur in this area the intercondyloid eminence was prominent and came in close contact with the femur, especially during the movements of semiflexion and extension. We are of the opinion that this observation is of importance in explaining the development of erosions in the area mentioned.

The posterior parts of the femoral condyles, which rest on the corresponding tibial surfaces during full flexion, showed erosions seven times on the medial condyles and five times on the lateral condyles. As

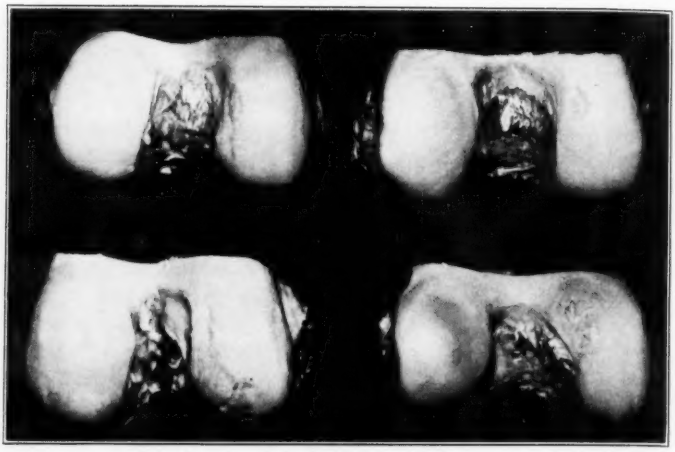

Fig. 7.—Photograph of the femoral condyles, showing erosions on the median aspect of the median condyle of the femur. This is the area of the femur which comes in contact with the intercondyloid tubercle of the median condyle of the tibia.

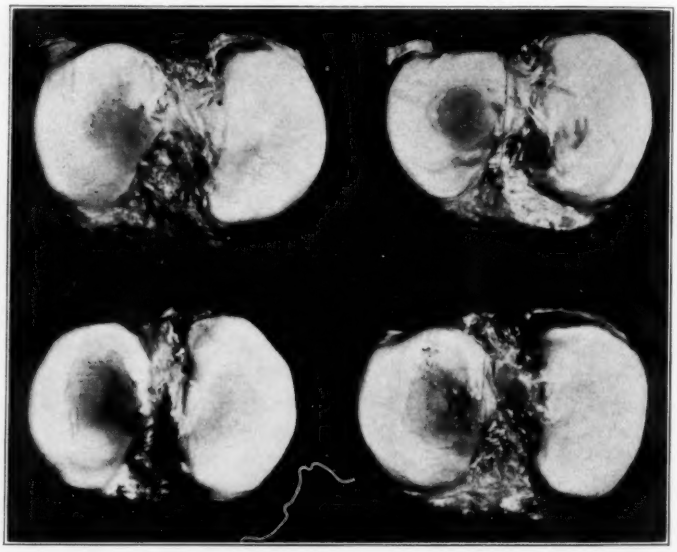

Fig. 8.—Photograph of the tibial condyles, showing areas of erosion. Note the erosions in the central part of the tibial condyles or the part of the surface which is uncovered by the semilunar cartilage.

the leg is in full flexion less frequently than in the other positions, these areas are in contact with one another less often. This probably accounts for the small number of erosions in this area.

Tibia.—The central portion of the lateral condyle of the tibia showed erosions or marked thinning of the cartilage in 64 cases, and the median condyle in 55 cases. The area of the tibial condyles which was covered by the menisci never showed erosions or thinning when the menisci were normal and were everywhere intact. When they were torn or displaced in such a way that they no longer protected the periphery of the tibia, erosions were frequently observed. Figure 8 illustrates the areas of the tibia usually involved. Here again it often was observed that the area of the tibia which was involved was opposite to an erosion on the corresponding articular surface of the femur.

Synovia.—The synovial membrane was smooth and glistening in 44 cases. In the remaining cases it ordinarily showed villous projections from the surface. It was not unusual to see the synovial membrane extending over the medial edge of the patella and, in many instances, projecting into the depressions made by the erosions in the cartilage. The villous projections increased in frequency with advancing age and were most striking in the patients with the most extensive alterations in joint structure.

COMMENT

From the data presented certain facts are clear. In the first place, anatomic changes in the knee joint were observed with increasing frequency with advancing age. The articular surface of the patella showed changes most often, and these changes were most conspicuous on the median articular facets. As we have said before, this is the part of the patella which comes in contact with the femur most often during such movements as walking. The interpatellar groove of the femur, or the area over which the patella glides, was the second most frequent site of erosion; then, in order, the lateral articular surface of the tibia, the median articular surface of the tibia and the median and the lateral condyles of the femur. On careful analysis it was obvious that the areas usually affected were those subjected to the greatest movement or weight, and this was particularly true of the points at which the articular surface came in contact during movement.

Previous observations have been made on the changes in the knee joints of patients who were not considered to be suffering from arthritis. Rimann [1] found changes in the joints of 67 of 100 persons between the ages of 15 and 80 who were examined at necropsy, and Beitzke,[2]

1. Rimann, H.: Arb. a. d. path. Inst. zu Berlin z. Feier **1**:139, 1906.

2. Beitzke, H.: Ueber die sogenannte Arthritis deformans atrophica, Ztschr. f. klin. Med. **74**:215, 1912.

on examining 200 bodies, found only 35 without alterations in some of the joints. Six showed anatomic changes of ordinary arthritis deformans, and in 16 there was evidence of gout. Of the remaining 178, visible changes were seen in the joints of 143. These changes were alike in the two sexes. Between the ages of 20 and 40 years 60 per cent of the joints showed changes; between 40 and 50 years, 95 per cent, and in older persons, 100 per cent. Clark [3] studied the lesions in the joints in 1,100 cases which came to autopsy in Panama; he found gross lesions in the joints in 15.6 per cent of the patients, and of these less than 1 per cent were considered to be suffering from arthritis. He emphasized syphilis, arteriosclerosis and hard work as important etiologic factors. The most recent observations are those of Heine,[4] who described the changes in 1,994 knee joints of patients varying from 15 to 89 years of age. Here again the changes increased with advancing age and varied from 1.5 per cent in the age period from 15 to 19 years to 100 per cent in the older age groups. The patella was involved most frequently and, as in our observations, the commonest point was the central or median facets. On the femur the interpatellar groove showed erosions most often, and the tibia was altered almost as frequently as the patella, the lateral condyle being involved more often than the median. In 490 cases, or 49 per cent, the changes were equal on both sides; in 35 per cent the right side showed greater changes than the left, and in 16 per cent the left side showed more changes than the right. The lesions occurred with equal frequency in males and females. It is evident, therefore, that in spite of the fact that the number of cases which we have observed is relatively small, lesions were observed in practically the same locations and with the same frequency by other investigators. Meyer [5] and Keyes [6] noted changes in the knee joints of cadavers which were similar to those observed by us, and Bennett and Bauer [7] made similar observations in patients who had no symptoms referable to the joints during life.

What has been said regarding the knee joint is true for other joints as well. According to Heine, the joints which show lesions most fre-

3. Clark, H. C.: Etiologic Factors in Gross Lesions of the Large Joints: Observations from 1,100 Consecutive Necropsies, J. A. M. A. **69**:2099 (Dec. 22) 1917.

4. Heine, J.: Ueber die Arthritis deformans, Virchows Arch. f. path. Anat. **260**:521, 1926.

5. Meyer, A. W.: Further Observations upon Use-Destruction in Joints, J. Bone & Joint Surg. **4**:491, 1922.

6. Keyes, E. L.: Erosions of the Articular Surfaces of the Knee Joint, J. Bone & Joint Surg. **15**:369, 1933.

7. Bennett, G. A., and Bauer, W.: A Systematic Study of the Degeneration of Articular Cartilage in Bovine Joints, Am. J. Path. **7**:399, 1931.

quently with increasing age are the knee, acromioclavicular, elbow, hip and metatarsal joints, the joints of the spine and the sternoclavicular and shoulder joints. Zöllner [8] and Smith-Petersen [9] have shown the same to be true in regard to the sacro-iliac joint. Sievers [10] studied the 77 acromioclavicular joints and obtained similar results. Ely [11] observed changes in the sternoclavicular joints at necropsy, although he did not state whether the alterations increased in frequency with advancing age.

From the recorded observations and from our own, it is difficult to escape the conclusion that the changes which are commonly observed in the joints with advancing age are precisely the same as those described as being characteristic of so-called degenerative arthritis. It is necessary, therefore, to inquire into some of the factors which have been held responsible for this disorder.

Degenerative arthritis is frequently considered to develop as the result of certain occupations. One of the first investigators to emphasize this point of view was Lane.[12] Since 1886 his observations have been confirmed repeatedly. Recently Fischer [13] and others made the interesting observation that degenerative arthritis commonly develops in the elbow and metacarpal and shoulder joints of men who work with compressed air hammers. The changes in the joints appear anywhere from three to ten years after work with these tools and Fischer was of the opinion that repeated small traumas from the constant jarring of the hammer are mainly responsible for the development of this disorder. On the other hand, Fischer was unable to demonstrate that arthritis in the knee was more common in any particular occupation. He pointed out, however, that workers who carry heavy weights and who work in a kneeling position get arthritis, but he considered that occupation alone was the cause in only a few cases. Of greater importance in accounting for the changes in the knee are static, functional

8. Zöllner, F.: Untersuchungen über die Erscheinungsformen der Arthritis deformans in den Sacro-Iliacalgelenken, Virchows Arch. f. path. Anat. **277**:817, 1930.

9. Smith-Petersen, M. N.: Traumatic Arthritis, Arch. Surg. **18**:1216 (April) 1929.

10. Sievers, R.: Arthritis deformans des Akromioklavikulargelenks: zugleich ein Beitrag zur traumatischen Entstehung der Arthritis deformans chronica, Virchows Arch. f. path. Anat. (supp. 1) **226**:123, 1919.

11. Ely, L. W.: A Study of the Sterno-Clavicular Joint, in Ely, L. W., and Cowan, J. F.: Bone and Joint Studies, Stanford University, Calif., Stanford University Press, 1916, p. 121.

12. Lane, W. A.: Some Points in the Physiology and Pathology of the Osseous Systems of Trunk and Shoulder Girdle, Guy's Hosp. Rep. **28**:321, 1886.

13. Fischer, A.: Rheumatismus als Berufskrankheit, Acta rheumatol. **4**:24, 1932.

or traumatic factors. Flatfeet and rachitic deformities of the hips or knees (coxa vara or genu valgum) were found to be of great importance in producing arthritis of the joints of the lower extremities. From a study of the occupation of our patients it was not possible to show any correlation between the changes in the knee joints and the type of work done by the patients, although complete details of the work are lacking. As the changes were the same in both sexes, it would appear that the alterations in the knee joints which we studied will have to be explained on some basis other than occupation. Heine was of the opinion that factors other than the type of occupation were accountable for the changes in the joints which he observed, but Pommer,[14] on the other hand, has repeatedly expressed the opinion that occupation is of great importance in degenerative arthritis, and he has quoted a number of observers who support this belief.

Of more importance than occupation in explaining the changes in the knee joints is the question of mechanical factors due to trauma, static defects and incongruities of the articular surfaces. The mechanico-functional theory of the production of the degenerative arthritis has received support from the observations of many investigators. Beneke,[15] as a result of his studies in spondylitis deformans, concluded that the primary change in this disorder was degeneration of the intervertebral disks and that the changes in the vertebra resulted from continuous trauma caused by the degeneration. It is known now that the intervertebral disk becomes less elastic with advancing age, as is shown by the decreasing water content of the nucleus pulposus and the narrowing of the intervertebral space. This allows the anterior part of the vertebral bodies to come in contact during movement so that lipping and the characteristic arthritic changes in the spine occur. These changes in the spine have been produced experimentally in dogs by Keyes and Compere [16] by reducing the intervertebral space so that the vertebral bodies impinged on one another during movement.

To Preiser [17] belongs the credit for having emphasized the great importance of static defects in producing degenerative arthritis. As a

14. Pommer, G.: Ueber die mikroskopischen Kennzeichen und die Entstehungsbedingungen der Arthritis deformans (nebst neunen Beiträgen zur Kenntnis der Knorpelknötchen), Virchows Arch. f. path. Anat. **263**:434, 1927.

15. Beneke, R.: Zur Lehre von der Spondylitis deformans, Versamml. d. deutsche Naturf. u. Aerzte, Braunschweig, 1897, p. 109.

16. Keyes, O. C., and Compere, E. L.: The Normal and Pathological Physiology of the Nucleus Pulposus of the Inter-Vertebral Disc, J. Bone & Joint Surg. **14**:897, 1932.

17. Preiser, Georg: Statische Gelenkerkrankungen, Stuttgart, Ferdinand Enke, 1911; Ueber die Arthritis deformans coxae; ihre Beziehungen zur Roser Nélatonschen Linie und über den Trochanter Hochstand, Hüftgesunder infolge abnormaler Pfannenstellungen, Deutsche Ztschr. f. Chir. **89**:591, 1907.

result of numerous clinical observations he demonstrated that static deformities cause incongruities of the articular surfaces which lead to abnormal pressure and weight in certain parts of the joint and to the subsequent changes due to the trauma caused by weight and movement. Pommer,[14] on the basis of extensive microscopic studies of the joints, proposed what is generally known as the "functional theory of Pommer." Instead of accepting the idea that the primary lesion in the joint is a degeneration of the cartilage or osteoporosis of the subchondral bone, he concluded that the first thing that happens is damage to the cartilage from trauma, with a loss of its elasticity, or that, if the cartilage has lost its elasticity as a result of the process of involution, it is more readily injured. When the elasticity of the cartilage is lost, the subchondral bone and its marrow are no longer protected from the irregular, localized effects of weight, pressure and impacts. This lack of protection and the subsequent trauma cause increased vascularization and ossification of the bone, with thickening and all the characteristic changes of degenerative arthritis. This theory of the development of degenerative arthritis has attracted widespread attention and interest, and there is ample clinical and experimental evidence available at present to support it. A few of the relevant facts are recalled.

There are numerous clinical examples of degenerative arthritis following trauma to the joints, with resulting incongruities of surface, static defects, abnormal weight bearing and pressure. A few of the more important ones may be cited.

When arthritis follows direct injury to a joint it is commonly called traumatic arthritis. When this occurs the clinical and pathologic features of the changes produced are sometimes indistinguishable from definite cases of degenerative arthritis in which no violent injury has occurred. For example, compressed fractures of one or both condyles of the tibia, with resulting genu valgum or varum, are invariably followed by changes in the knee joint characteristic of degenerative arthritis. In these cases the abnormal distribution of weight on one or the other tibial condyle, together with displacement of the patella, causes degenerative changes. Another example of such an occurrence is arthritis of the elbow joint developing as a result of fractures of the head or neck of the radius, with displacement of the head. If the displacement is not corrected or if the fractured bone is not removed, arthritis always appears sooner or later.

A further example of arthritis developing after an injury is its appearance following Legge-Perthes' disease or osteo-arthritis deformans juvenilis. As a result of the extensive researches of Lang[18] and the

18. Lang, F. S.: Osteo-Arthritis Deformans Contrasted with Osteo-Arthritis Deformans Juvenilis, J. Bone & Joint Surg. **14**:563, 1932.

recent studies of Freund [19] and of Miltner and Hu,[20] there seems to be little doubt that this disorder of the hip joint occurs as a result of direct or indirect traumatic damage to the cartilage, particularly at the osteochondral junction. This seems to be particularly striking if the blood supply through both the ligamentum teres and the periosteum is interfered with at the same time. The histologic picture is not unlike that seen in adults with osteo-arthritis of the hip joint, and with healing the deformity of coxa vara is commonly observed. The sequence of events in the healing of the process has recently been studied in detail by means of the roentgen ray by Freund.[19] Key [21] called attention to the deformity of the hip joint following the slipping of the upper femoral epiphysis in adolescence. In these cases the head of the femur is displaced so that it no longer forms a perfect ball and socket joint, and sooner or later, usually in adult life, pain and limitation of motion in the hip appear as a result of the changes following the mechanical defect.

Fractures of bones other than the ones mentioned may be followed by arthritis, for example, arthritis of the ankle joints following fracture of the os calcis and arthritis of the wrist joint following fractures of the lower end of the radius.

Arthritis following an injury to the hip joint may be seen in cases of posttyphoid coxitis. It is well recognized that when typhoid fever is complicated by arthritis the spine and hip are most commonly involved. When the hip is affected, subluxation or partial dislocation frequently occurs. This leads to a deformity of the head of the femur and acetabulum, and changes not unlike those seen in degenerative arthritis follow.

Charcot's Joints.—The alterations in so-called Charcot's joints must be regarded as nothing more or less than the results of frequent traumas to joints which have been rendered insensitive to pain by loss of the sensation of pain and the sense of position. There is overwhelming experimental and clinical evidence to support this view . The excellent review of the clinical aspects of the lesions in the joints caused by nerve lesions, as detailed by Shands,[22] and the recent thorough histologic study of Charcot's joints by Moritz [23] leave no doubt that the lesions are

19. Freund, E.: Zur Deutung des Röntgenbildes der Perthesschen Krankheit, Fortschr. a. d. Geb. d. Röntgenstrahlen **42**:435, 1930.

20. Miltner, L. J., and Hu, C. H.: Osteochondritis of the Head of the Femur; An Experimental Study, Proc. Soc. Exper. Biol. & Med. **30**:416 (Jan.) 1933.

21. Key, J. A.: Traumatic Arthritis and the Mechanical Factors in Hypertrophic Arthritis, J. Lab. & Clin. Med. **15**:1145, 1930.

22. Shands, A. R., Jr.: Neuropathies of the Bones and Joints, Arch. Surg. **20**: 614 (April) 1930.

23. Moritz, A. R.: Tabische Arthropathie, Virchows Arch. f. path. Anat. **267**:746, 1928.

the result of repeated trauma to the joints. It should be emphasized that in many instances the changes in the joints are extensive owing to the excessive trauma that follows the loss of the sensation of pain. It is only natural to find less extensive changes following trauma to a joint in a person with intact sensation of pain for the reason that once the joint has been injured it is not used so much as a joint devoid of the sensation of pain. In some cases the changes produced by trauma are further exaggerated by a secondary invasion of the joint by bacteria. This occurs particularly if there are decubitus ulcers around the joints, such as the ankle joints.

Hemophilia.—One of the outstanding features of hemophilia is hemorrhage into the joints. This commonly follows slight trauma. Keefer and Myers [24] have emphasized that the changes brought about by repeated trauma and hemorrhage into the joints in patients with hemophilia were often indistinguishable from those of degenerative arthritis. In these cases, there is little doubt that the influences of the hemorrhage resulting from slight injury are capable of producing the derangements of the joints.

Aside from these clinical observations, there are a number of carefully controlled experiments on animals which support the hypothesis that degenerative arthritis results from frequent traumas to opposing articular surfaces. They are reviewed briefly.

Experimental Degenerative Arthritis.—Numerous attempts have been made to reproduce the gross and microscopic changes of degenerative arthritis in animals. A variety of methods have been used, but the favorite ones have been those which damage the cartilage and subchondral bone. Other methods, such as the production of a decreased blood supply and of increased pressure on the surfaces of the joints, and the displacement of articular surfaces so that they are no longer mutually adapted to one another have been employed.

The most recent work in America has been done by Key [21] and by Bennett, Bauer and Maddock.[25] They studied the changes in the joints following the production of defects in the articular cartilage and noted alterations which were similar to those occurring in degenerative arthritis. Bennett, Bauer and Maddock were able to produce this picture with absolute regularity only when the patella became displaced following operation. When the defects in the cartilage of the femur were produced and the patella did not become displaced, the joints

24. Keefer, C. S., and Myers, W. K.: Hemophilic Arthritis, New England J. Med. **208**:1183 (June 8) 1933.

25. Bennett, G. A.; Bauer, W., and Maddock, J. J.: A Study of the Repair of Articular Cartilage and the Reaction of Normal Joints of Adult Dogs to Surgically Created Defects of Articular Cartilage; "Joint Mice" and Patellar Displacement, Am. J. Path. **8**:499, 1932.

remained essentially normal, except for the area damaged by the operation. These experiments are of the highest importance in showing the effect of incongruities of articular surfaces in producing degenerative arthritis. Other observers, notably, Axhausen [26] and Ely and Cowan,[27] produced changes in cartilage and bone similar to those seen in degenerative arthritis by destroying the cartilage with chemicals or with a knife. In some cases border exostoses were produced, but never with regularity. Other forms of trauma, such as freezing the joints and injury by percussion with a rubber hammer, have been used to produce arthritic changes in the joints, with reasonable success.

The effect of abnormal pressure on articular surfaces has been investigated by Müller.[28] He sutured the humeri of rabbits to the scapula and immobilized the shoulder so that the tendon of the biceps was in contact with the cartilage of the humerus. The result of these experiments was an erosion of the cartilage and changes in the bone caused by pressure. He did not observe the characteristic alterations of degenerative arthritis and concluded that the functional factors involved in movement following trauma were of importance in the production of lesions. When he produced loosening of the epiphysis and subluxation of the head of the femur in different animals a necrotizing and repair process on the head of the femur appeared, with the typical findings of degenerative arthritis.

Key [21] tested the effect of abnormal strain on joints by attempting to produce knock-knee in rabbits. In the animals in which the patella was displaced outward so that it rested on the femoral condyle chronic arthritis developed, with border exostoses. In these animals other disturbances than displacement of the patella had been produced during the manipulations; the lower end of the femur had been fractured, the epiphysis had slipped or the cruciate ligaments had been torn. In other words, damage to the joints as well as the mechanical strain produced by the lack of mutually adapted articular surfaces were important in producing the picture.

Aside from the fact that trauma, mechanical strain and surface irregularities are essential for the experimental production of arthritic changes in the joints, movement of the damaged joint is of the highest importance in determining the anatomic picture. This feature has been investigated at length by Burckhardt.[29] He injured the cartilage of

26. Axhausen, Georg: Arch. f. klin. Chir. **99**:519, 1912.

27. Ely, L. S., and Cowan, J. F.: Bone and Joint Studies, Stanford University, Calif., Stanford University Press, 1916, p. 38.

28. Müller, W.: Experimentelle Untersuchungen über Druckusuren an Gelenkenden für die Pathogenese der Arthritis deformans, Deutsche Ztschr. f. Chir. **180**:203, 1923.

29. Burckhardt, H.: Experimentelle Untersunchungen über die Beziehungen der Gelenkfunktionen zur Arthritis deformans, Arch. f. klin. Chir. **132**:706, 1924.

the joints with phenol and studied the changes which developed in those which were immobilized by paralysis of the extremities by cutting the nerve plexus; he compared them with joints which were similarly injured but which were allowed to move. The final picture was different. In the joints which were immobilized the cartilage was gradually replaced by connective tissue and new cartilage which tended to fill the joint cavity and produce ankylosis. The connective tissue (pannus) grew into the articular space from the periphery of the joint, and exostoses were never observed. In the joints which were not immobilized exostoses developed, and the picture was similar to that seen in typical degenerative arthritis.

The experiments of Müller, cited previously, likewise emphasize the importance of movement in producing the characteristic changes in the joints. As he never produced characteristic lesions in immobilized joints he emphasized the importance of the functional aspect of disease of the joints.

In view of these observations, it seems well established that the lesions of degenerative arthritis may be reproduced in animals by a variety of methods which injure cartilage and bone and alter normal articular function. The picture which is characteristic of degenerative arthritis, then, is the result of the process of repair to damaged tissues of the joint.

From our observations and from those of other investigators, it seems difficult to escape the conclusion that the changes which are seen in the joints with increasing frequency with advancing age are identical with those which have been previously described as characteristic of degenerative arthritis. If this is true, there is justification for the belief that degenerative arthritis is a process associated with the aging of the tissues of the joints. This conception is essential for a complete understanding of the pathogenesis of this disorder. Added to the process of involution, such factors as gross trauma, hemorrhage and static deformities exaggerate the condition. The end-result depends on the summation of these factors.

SUMMARY AND CONCLUSIONS

In a study of 100 knee joints from 77 consecutive patients who died of various diseases the following facts were determined:

1. Anatomic changes were noted with increasing frequency with advancing age.

2. The patella showed alterations in 81 per cent of the cases, the interpatellar groove in 65 per cent, the lateral condyle of the tibia in

64 per cent, the medial condyle of the tibia in 55 per cent, the medial condyle of the femur in 43 per cent and the lateral condyle in 36 per cent.

3. The erosions were commonest over the areas of contact which were subjected to the greatest movement, strain, weight-bearing and injury.

4. The changes were identical in males and females, and there was no relationship between the extent of the lesions in the joints and the symptoms referable to the joints.

5. There was no correlation between the lesions in the joints and the degree of arteriosclerosis or any other particular type of disease process.

6. The gross anatomic changes were indistinguishable from those previously described in degenerative arthritis.

7. The various factors which are of importance in the development of degenerative arthritis are discussed. They include the aging of tissue, wear and tear, strain, trauma, occupation and static deformities.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

III. HEMOGLOBIN AND CELL VOLUME COEFFICIENTS; ERYTHROCYTE VOLUME, HEMOGLOBIN CONTENT AND CONCENTRATION; COLOR, VOLUME AND SATURATION INDEXES

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Innumerable articles about the anemia of pregnancy have been published, but, although these reports presuppose a knowledge of the normal changes in the blood incident to pregnancy, so far as we know, complete hematologic studies made on the same women throughout pregnancy are not available. Therefore, as a preliminary to an investigation of the true anemia of pregnancy, we made serial hematologic studies of the blood of the same women during pregnancy and the puerperium.

Haden,[1] Osgood and Haskins,[2] Wintrobe[3] and others have determined the variations and averages in normal nonpregnant women. Their work demonstrates that the average erythrocyte has a definite volume and a definite content of hemoglobin, and that the hemoglobin forms a definite proportion of the cell. They discussed the importance of the color index, but stated that in addition the volume and saturation indexes together with the data for the average cell are of the utmost importance in a study of the blood. They stated that the volume index in pernicious anemia may be much greater in the early stages, when the count is relatively high, than in the later stages, when the count is low, thus indicating its value as an early diagnostic test.

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1. Haden, R. L.: The Value of Volume Index in the Diagnosis of Pernicious Anemia, J. A. M. A. **83**:671 (Aug. 30) 1924.

2. Osgood, E. E., and Haskins, H. D.: Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women; Redeterminations of Color Index, Volume Index and Saturation Index Standards Based on Observations in One Hundred Cases, Arch. Int. Med. **39**:643 (May) 1927.

3. Wintrobe, M. M.: Blood of Normal Young Women Residing in Subtropical Climate, Arch. Int. Med. **45**:287 (Feb.) 1930.

The relationship between the absolute cell determinations and the three indexes is best shown, graphically, by Wintrobe.

$$\frac{\text{Volume (cc. per 1,000 cc.)}}{\text{R. B. C. (in millions)}} = \text{Corpuscular volume in cc.} \times 10^{-12} \text{ or cubic microns } (c.\mu.) \quad \left| \quad \frac{\text{Volume per cent}}{\text{R. B. C. per cent}} = \text{Volume index} \right.$$

$$\frac{\text{Hemoglobin (Gm. per 1,000 cc.)}}{\text{R. B. C. (in millions)}} = \text{Mean corpuscular hemoglobin in Gm.} \times 10^{-12} \text{ or micromicrograms } (\gamma\gamma) \quad \left| \quad \frac{\text{Hemoglobin per cent}}{\text{R. B. C. per cent}} = \text{Color index} \right.$$

$$\frac{\text{Hemoglobin (Gm. per 100 cc.} \times 100)}{\text{Volume (cc. per 100 cc.)}} = \text{Mean corpuscular hemoglobin concentration \%} \quad \left| \quad \frac{\text{Hemoglobin per cent}}{\text{Volume per cent}} = \text{Saturation index} \right.$$

It is evident from the nature of these equations that all indexes must approximate unity in normal persons. The standard blood contains 14.3 Gm. of hemoglobin and 43 cc. of packed cells for each hundred cubic centimeters of blood and 5 million erythrocytes per cubic millimeter. These figures were derived from a study of one hundred women by Osgood and Haskins, and of fifty women by Wintrobe; the results were essentially the same (hemoglobin, 14.2; cells, 42.8). The variations of the indexes from unity, according to Haden, seldom exceed 5 per cent in normal adults. The color index in primary anemia is usually greater and seldom less than unity, while in secondary anemias from any cause it is lower. Haden, Osgood,[4] Wintrobe, and others claimed that the volume index is a more accurate criterion of the types of anemia and stated that greater diagnostic information can be gained by a comparison of all three indexes. Peters and Van Slyke[5] stated that the saturation index is of doubtful value in differentiating anemias because it is dependent partly on total electrolyte concentration and partly on the reaction or bicarbonate content of the blood.

Serial blood volume, hemoglobin, hematocrit and erythrocyte determinations were made on a group of women, designated as series A, beginning in the first trimester of pregnancy and continuing up to two weeks post partum. Another group, on whom the first determinations were made at term but continued up to eight weeks post partum, is designated as series B. In addition, groups of patients were studied at the different periods of pregnancy and the puerperium.

The methods which have been described in previous articles are all standard, and the accuracy is as great as is feasible. Hemoglobin,

4. Osgood, Edwin E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standard; Redeterminations Based on Findings in One Hundred and Thirty-Seven Healthy Young Men, Arch. Int. Med. **37**:685 (May) 1926.

5. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

hematocrit and erythrocyte determinations were converted to percentage of normal (hemoglobin, 14.3; hematocrit, 43; erythrocytes, 5 million) before the indexes were calculated.

In table 1 are listed the variations and averages for the color index. There is a small increase in the average color index during pregnancy, with a decrease at term and a still further decrease post partum. However, the entire change is within the normal variation. The wide range from 0.80 to 1.44 in normal pregnant or puerperal women indicates that one must be cautious in the diagnosis of anemia during pregnancy. This increase in the color index, which is best shown in the individual cases in table 4, indicates an increase in the hemoglobin, which may be

TABLE 1.—*Color Index: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
0.80-0.89	..	1	3	7	4	6	2
0.90-0.99	7	..	2	15	2	12	3
1.00-1.09	7	7	4	15	6	9	5
1.10-1.19	7	1	10	11	10	6	1
1.20-1.29	4	..	4	2	1	3	..
1.30-1.44	..	..	2	3	2	4	..
Total	25	9	25	53	25	40	11
	Averages						
Total cases	1.07*	1.04	1.10	1.04	1.07	1.04	0.97
Series A	1.07	....	1.08	0.98	....	1.01	....
Series B	....	....	....	1.00	0.99	....	0.96

* The normal range was from 0.90 to 1.10.

either absolute or relative. The former is unlikely, while the latter necessitates an increase in the size of the cell, which does occur.

In table 2 are listed the variations and averages for the volume index. The averages indicate an increase in the size of the cell during pregnancy and a decrease at term, with a still further decrease post partum. The wide range again indicates that caution must be used in the interpretation.

In table 3 are listed the variations and averages for the saturation index. These figures show marked variation, but a less wide digression from unity. This index of approximately 1 indicates that the hemoglobin content is only relatively increased.

In table 4 are listed the variations and averages for the individual cell volume in cubic microns. The volume remains within normal limits, but it is clearly evident that there is a definite increase in the size of the cell, reaching a maximum at from twenty-six to thirty-five weeks,

TABLE 2.—*Volume Index: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
0.80-0.89	1	..	..	2	..	1	2
0.90-0.99	6	2	3	9	5	9	3
1.00-1.09	11	5	6	23	7	16	6
1.10-1.19	6	2	13	17	7	10	..
1.20-1.29	1	..	3	1	4	3	..
1.30-1.44	..	..	..	1	1	2	..
Total	25	9	25	53	24	41	11
	Averages						
Total cases	1.07*	1.05	1.11	1.05	1.10	1.02	0.98
Series A	1.04	....	1.10	1.04	....	1.09	....
Series B	....	....	....	1.04	1.04	0.96	0.98

* The normal range was from 0.90 to 1.10.

TABLE 3.—*Saturation Index: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
0.80-0.89	..	2	3	7	2	6	1
0.90-0.99	13	2	5	22	10	19	4
1.00-1.09	8	4	19	23	12	17	6
1.10-1.19	5	1	..	4	..	2	..
Total	26	9	27	56	24	44	11
	Averages						
Total cases	1.02*	0.99	0.99	0.99	1.12	0.98	0.99
Series A	1.04	....	0.99	0.95	....	0.95	....
Series B	....	....	....	0.96	0.95	0.93	0.99

* The normal range was from 0.90 to 1.10.

TABLE 4.—*Individual Cell Volume, Cubic Microns: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Cubic Microns	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
70- 79	1	..	..	4	2	1	2	3
80- 89	12	4	6	24	8	14	3	5
90- 99	10	4	14	20	9	7	3	3
100-109	2	1	3	4	5	5	2	..
110-120	..	..	1	1	..	2	..	..
Total	25	9	24	53	24	29	10	11
	Averages *							
Total cases	90.0†	89.5	94.0	90.3	93.8	91.3	90.1	84.2
Series A	89.9	....	94.0	89.2	...	93.6	....	....
Series B	....	....	....	88.6	89.1	82.0	....	84.1

* The normal average was 88.2 cubic microns.
† The normal range was from 80 to 100 in 24 patients.

a slight decrease at term and a still further decrease post partum. All changes, however, are within the normal limits.

In table 5 are listed the average hemoglobin and volume coefficients and the erythrocyte volume and hemoglobin content, both in grams and in percentage values, for series A and B. These coefficients are obtained with the following equations:

$$\text{Hemoglobin coefficient} = \frac{\text{hemoglobin} \times 5}{\text{R. B. C. (in millions)}} = \text{grams of hemoglobin per 5 million cells}$$

$$\text{Volume coefficient} = \frac{\text{hematocrit} \times 5}{\text{R. B. C. (in millions)}} = \text{cc. of cells per 5 million cells}$$

These data indicate that in the period of from ten to thirty-five weeks the erythrocytes differ from the average normal in that they are a little

TABLE 5.—*Average Hemoglobin and Volume Coefficients and Corpuscular Volume and Hemoglobin Content for Series A and B During Pregnancy and the Puerperium*

	Ante Partum, Weeks				Post Partum		
			36 to Term		10 to 25 Days		
	10 to 15 A	26 to 35 A	A	B	A	B	8 Weeks B
Hemoglobin coefficient, Gm. (Normal = 14.3)	15.5	15.7	14.2	14.2	14.6	13.4	13.8
Volume coefficient, cc. (Normal = 43.0)	45.1	47.3	44.9	44.5	47.1	41.8	42.3
Corpuscular:							
Volume, (c.μ.) (Normal = 88)	90.0	94.0	89.0	89.0	94.0	82.0	84.0
Hemoglobin 10^{-12}, Gm. (Normal = 28.6)	30.4	29.7	28.6	28.5	27.2	26.9	27.7
Hemoglobin proportion, % (Normal = 32.5)	34.2	32.9	32.5	31.9	31.1	32.2	32.7

larger and contain more hemoglobin, and, as a result, the volume and hemoglobin coefficients are definitely increased. At term the various constants are essentially normal. At from ten to twenty-five days post partum, the figures for series A are essentially normal, with the exception of the cell volume, which is again increased. At eight weeks, the figures indicate a slightly smaller cell, with a normal concentration of hemoglobin, but a decreased amount, resulting in hemoglobin and volume coefficients which are also slightly decreased. An analysis of the data in this table indicates that there are marked changes in the erythrocytes in pregnancy, suggestive of a beginning primary anemia, especially between the tenth and the thirty-fifth week. The increase in the size of the cell between the twenty-sixth and the thirty-fifth week is probably a compensatory one, because the so-called physiologic anemia is greatest at this time.

In tables 6 and 7 are included essential data on series A and B. A detailed analysis of the results is unnecessary, but the individual varia-

TABLE 6.—*Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)*

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Hemoglobin Coefficient, Gm.	Volume Coefficient, Cc.	Corpuscular			Indexes		
				Volume, (c.μ.)	Hemoglobin				
					10^{-12} Gm.	Proportion in Cell, %	Color	Volume	Saturation
1	13 wks.	14.8	42.9	85	29.6	34.5	1.03	1.00	1.03
II	29 wks.	16.2	49.2	98	32.4	32.9	1.14	1.14	1.00
W	40 wks.	12.8	43.8	87	25.5	29.1	0.89	1.01	0.88
20	12 days	13.2	42.9	85	26.5	30.8	0.93	1.00	0.93
2	14 wks.	13.9	42.1	84	27.8	33.1	0.90	0.91	0.99
I	30 wks.	15.6	47.2	91	31.3	33.1	1.09	1.09	1.00
W	40 wks.	13.2	43.5	89	26.4	30.3	0.93	1.01	0.91
23	12 days	13.6	43.2	86	27.2	31.4	0.95	1.00	0.95
3	15 wks.	18.2	48.1	96	36.5	37.9	1.28	1.12	1.14
I	30 wks.	19.1	55.4	110	38.3	34.5	1.33	1.29	1.03
W	40 wks.	13.6	47.4	94	27.2	28.6	0.95	1.10	0.86
23	12 days	....	....	...	....	....	....	....	1.09
4	14 wks.	14.5	41.8	83	36.6	28.8	1.02	0.97	1.05
VII	27 wks.	14.8	42.9	85	33.8	34.5	1.03	1.03	1.03
W	40 wks.	....	....	...	....	....	....	....	0.99
30	14 days	13.2	44.6	89	31.8	30.0	0.92	1.03	0.88
5	12 wks.	16.0	46.5	92	31.2	34.5	1.12	1.09	1.03
II	28 wks.	15.0	45.9	91	27.0	32.6	1.05	1.06	0.99
W	39 wks.	13.3	44.4	89	25.7	30.0	0.93	1.02	0.91
25	14 days	12.3	48.2	96	20.1	25.5	0.86	1.11	0.77
6	14 wks.	14.0	44.3	88	25.7	31.7	0.99	1.04	0.95
I	27 wks.	16.0	48.7	97	25.7	32.9	1.13	1.13	1.00
W	40 wks.	12.5	38.8	77	32.2	32.1	0.88	0.91	0.97
19	11 days	16.7	45.8	91	33.4	36.4	1.16	1.06	1.09
7	14 wks.	17.4	53.2	106	24.6	32.8	1.22	1.24	0.99
VI	30 wks.	16.6	46.5	93	26.9	34.8	1.14	1.09	1.05
W	40 wks.	16.0	48.9	97	26.8	32.8	1.12	1.13	0.99
31	5 days	18.5	53.4	106	23.4	34.7	1.31	1.25	1.05
	13 days	20.4	60.3	120	20.7	33.8	1.44	1.41	1.02
8	14 wks.	16.3	42.4	84	31.8	38.6	1.14	0.98	1.17
III	28 wks.	17.4	49.2	98	26.6	35.4	1.23	1.13	1.07
C	40 wks.	14.7	43.8	85	29.9	33.6	1.03	1.02	1.01
30	11 days	11.9	40.0	80	23.8	30.0	0.84	0.93	0.91
9	14 wks.	14.4	46.4	92	28.8	31.1	1.00	1.08	0.93
I	29 wks.	16.8	47.5	94	33.5	35.3	1.17	1.10	1.07
C	40 wks.	14.7	46.6	93	29.4	40.8	1.02	1.07	0.95
21	3 days	15.6	47.5	95	31.3	32.9	1.10	1.10	1.00
	12 days	16.5	50.1	100	32.9	32.9	1.14	1.17	0.98
10	20 wks.	16.5	46.1	92	31.8	34.5	1.05	1.07	0.98
I	36 wks.	16.5	44.8	89	33.0	36.8	1.14	1.04	1.10
W	3 days	17.3	47.8	95	34.7	36.3	1.17	1.11	1.05
26									
11	15 wks.	16.7	49.4	96	33.3	34.4	1.16	1.13	1.03
I	28 wks.	12.9	44.1	88	25.8	29.2	0.91	1.03	0.88
W	39 wks.	13.3	43.1	86	26.5	30.8	0.93	1.01	0.92
22	12 days	15.6	51.9	103	31.1	30.0	1.02	1.20	0.85
12	9 wks.	14.0	38.5	76	28.0	36.3	0.92	0.89	1.03
I	27 wks.	11.0	41.6	83	22.0	26.5	0.76	0.96	0.79
C	40 wks.	15.0	44.1	88	29.9	33.9	1.04	1.02	1.01
28	11 days	12.5	43.1	86	24.9	28.9	0.88	1.00	0.88
13	11 wks.	....	....	...	....	36.4	....	....	1.09
VII	29 wks.	15.6	50.7	101	31.2	30.8	1.10	1.18	0.93
C	40 wks.	15.1	49.5	98	30.2	30.6	0.96	1.15	0.83
37	11 days	....	....	...	....	32.9	....	....	0.99
22	16 wks.	16.9	48.9	97	33.7	34.5	1.14	1.16	0.98
II	28 wks.	17.1	47.1	94	34.3	36.4	1.20	1.10	1.08
W	40 wks.	....	....	...	....	32.1	....	....	0.97
24	12 days	....	....	...	....	32.3	....	....	0.98

* W denotes white race; C, colored race.

tions during pregnancy are so marked that it is evident that a diagnosis of anemia requires more than a hemoglobin or erythrocyte determination and that, even with a complete hematologic examination, in many cases the diagnosis will still be questionable.

TABLE 7.—*Data on Patients Followed from Term to Eight Weeks Post Partum (Series B)*

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Hemoglobin Coefficient, Gm.	Volume Coefficient, Cc.	Corpuscular			Indexes		
				Volume, (c.μ.)	Hemoglobin 10^{-12} Gm.	Hemoglobin Proportion in Cell, %	Color	Volume	Saturation
31	39 wks.	13.3	42.2	84	26.6	31.5	0.93	0.99	0.95
I	12 days	13.6	41.5	83	27.3	32.9	0.95	0.97	0.98
C	8 wks.	15.4	44.2	88	30.7	34.8	1.07	1.02	1.05
15									
32	40 wks.	16.1	49.1	98	32.2	32.8	1.12	1.15	0.98
I	3 days	16.6	48.6	97	33.1	34.1	1.15	1.12	1.03
W	12 days	12.0	41.7	83	24.1	28.9	0.84	0.98	0.86
27	8 wks.	13.6	39.3	78	27.1	34.5	0.94	0.91	1.03
33	40 wks.	16.6	48.2	96	33.1	34.4	1.17	1.12	1.04
II	3 days	14.3	42.9	85	28.6	33.3	1.00	1.00	1.00
W	19 days	13.1	39.3	78	26.2	33.3	0.91	0.91	1.00
29	9 wks.	14.8	41.9	83	30.0	35.3	1.04	0.98	1.06
34	40 wks.	16.1	44.4	88	32.2	36.3	1.12	1.03	1.09
I	5 days	14.0	40.6	81	28.1	34.5	0.98	0.95	1.04
C	8 wks.	14.0	45.6	91	28.0	30.8	0.98	1.06	0.92
25									
35	36 wks.	13.2	44.1	88	26.5	30.0	0.93	1.02	0.91
II	11 days	13.2	39.7	73	26.3	33.1	0.80	0.80	1.00
W	8 wks.	12.9	42.4	84	25.9	30.5	0.90	0.98	0.92
24									
36	40 wks.	12.4	42.8	85	24.9	29.1	0.87	0.99	0.88
I	3 days	10.4	39.0	78	20.7	26.5	0.72	0.90	0.80
C	12 days	13.2	40.2	80	26.4	32.8	0.92	0.94	0.98
25	8 wks.	10.0	35.5	70	20.0	28.3	0.70	0.82	0.85
37	38 wks.	12.6	43.4	86	25.2	28.9	0.89	1.01	0.88
III	12 days	12.2	43.3	86	24.4	28.2	0.86	1.01	0.85
W	8 wks.	12.0	38.1	76	24.0	31.4	0.84	0.88	0.95
30									
39	39 wks.	15.6	46.8	93	31.2	33.3	1.09	1.09	1.00
I	11 days	14.4	45.6	91	28.7	31.5	0.95	1.06	0.90
W	17 wks.	15.1	43.8	87	30.2	34.5	1.05	1.02	1.03
17									
40	40 wks.	12.5	41.0	82	25.1	30.6	0.86	0.95	0.92
III	3 days	15.1	46.1	91	30.3	32.9	1.00	1.08	0.93
C	25 days	14.8	40.9	81	29.5	36.4	1.02	1.06	1.08
28	8 wks.	15.3	46.1	92	30.6	33.2	1.02	1.07	0.95
43	38 wks.	14.0	43.2	86	27.9	32.3	0.98	1.01	0.97
I	5 days	16.3	51.8	103	32.7	31.5	1.10	1.20	0.92
C	19 days	14.4	43.8	87	28.8	32.9	0.95	1.02	0.93
17	8 wks.	15.3	46.0	92	30.5	33.2	1.06	1.06	1.00

* W denotes white race; C, colored race.

CONCLUSIONS

Calculations of the various indexes, coefficients and absolute cell determinations of the blood during pregnancy and the puerperium indicate: 1. There are marked individual variations of all the indexes, especially of the color index, but the average for each remains close to unity.

2. The corpuscular volume is increased slightly between the twenty-sixth and the thirty-fifth week, when the anemia is at its maximum. There is another slight increase during the first week post partum, when a slight anemia is also present.

The hemoglobin and volume coefficients are increased during the greater part of pregnancy, but they are essentially normal at term and during the puerperium.

The corpuscular hemoglobin is increased slightly both in amount and in percentage during the greater part of pregnancy, but it is normal at term and during the puerperium.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

IV. PERCENTAGES AND GRAMS PER KILOGRAM OF SERUM PROTEIN AND FIBRIN AND VARIATIONS IN TOTAL AMOUNT OF EACH

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Many reports of changes in serum protein and fibrin in pregnancy have been published, but a study of the data indicates that the results are not uniform. The majority of the reports indicate that there is a decrease in serum protein and an increase in fibrin. Serial determinations of these substances on the same women throughout pregnancy and the puerperium should definitely demonstrate the direction and degree of change. Furthermore, the determination of the plasma volume on these same patients should make it possible to determine the total amount of serum protein and fibrin, the amounts per kilogram and the variations in total amount in each. Thus, the question of changes in protein in pregnancy would be settled, and some information as to the cause of the physiologic edema of pregnancy and of edema in general might be obtained.

In table 1 are listed some of the published data on the average percentages of serum protein and fibrin in nonpregnant and pregnant women (minimum figures for the latter). It is surprising to note the small number of patients used by the different investigators. With but two exceptions, all the reports indicate that in pregnancy the serum protein is decreased and the fibrin increased. The marked variations are due to the methods used. Refractometric determinations of protein yield high results unless the refraction of the nonprotein portion of each serum is also determined. This is done by the Robertson refractometric method, and the results can be compared with those obtained by the digestion method (Kjeldahl). The Wu method gives results which are relatively consistent and show the direction and degree of change, but cannot be compared with other methods because of inherent technical errors. The Kjeldahl method, in which the total and the

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TABLE 1.—*Reported Averages for Percentage of Serum Protein and Fibrin in Nonpregnant and Pregnant Women* *

		Nonpregnant			Pregnant			
	Year	Number of Patients	Serum Protein, per Cent	Fibrin, per Cent	Number of Patients	Serum Protein, per Cent, Minimum Average	Fibrin, per Cent, Maximum Average	Method
Rowe (Arch. Int. Med. **18**: 455, 1916)	1916	22 H	7.50	....	..	....	....	Refractometric, Robertson
Linder, Lundsgaard and Van Slyke (J. Exper. Med. **39**: 887, 1924)	1924	8	6.73	....	..	....	....	Macro-Kjeldahl
Salvesen (Acta med. Scandinav. **65**: 147, 1926)	1926	16	7.02	....	..	....	....	Macro-Kjeldahl
Howe (Physiol. Rev. **5**: 439, 1925)	1925	..	7.50	....	..	....	....	Macro-Kjeldahl
Peters et al. (J. Biol. Chem. **67**: 141, 1926)	1926	15	6.50 P	....	..	....	....	Macro-Kjeldahl
Bruckman, D'Esopo and Peters (J. Clin. Investigation **8**: 591, 1930)	1929	8	7.61	....	..	....	....	Macro-Kjeldahl
Starlinger and Winands (Ztschr. f. d. ges. exper. Med. **60**: 138, 1928)	1928	16	7.78 P	0.25	..	....	....	Refractometric, Reizz
Starlinger	1928	Review	8.00 P	0.25	..	....	....	
Rowe	1916	Review	7.94	....	..	....	....	
Cameron (Textbook of Biochemistry, ed. 3, New York, The Macmillan Company, 1931)	1931	Review	6.7 to 8.2	0.30 to 0.60	..	....	....	
Hawk and Bergeim (Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931)	1931	Review	6.5 to 8.2	0.30 to 0.60	..	....	....	
Zangemeister [3]	1903	2	8.15	....	6	6.32	Increased	Kjeldahl
Landsberg (Arch. f. Gynäk. **92**: 693, 1910)	1910	8	7.01	....	18	6.54	0.44	Kjeldahl
Dienst (Arch. f. Gynäk. **109**: 669, 1918)	1918	9	7.17	0.34	9	6.58	0.49	Kjeldahl, gravimetric
Mahnert [7]	1921	10	8.48	....	10	6.52	....	Refractometric, Reizz
Hafner (Arch. f. exper. Path. u. Pharmakol. **101**: 335, 1924)	1924	..	....	....	6	Increased	....	Refractometric, Reizz
Plass and Bogert [6a]	1924	22	7.04 P	....	88	6.27	....	Macro-Kjeldahl
Plass and Matthews [6c]	1926	15	7.42 P	0.31	144	7.04	0.38	Wu method, colorimetric
Coetzee (Proc. Roy. Soc. Med. **18**: 28, 1924)	1924	..	7.73 P	0.32	35	Reduced	0.52	Wu method, colorimetric
Kraul (Monatschr. f. Geburtsh. u. Gynäk. **70**: 6, 1925)	1925	..	....	0.25	50	6.50	0.50	Refractometric
Eufinger (Klin. Wchnschr. **7**: 492, 1928)	1928	..	8.50	0.15	36	6.66	0.24	Refractometric, Reizz
Runge and Kessler (Arch. f. Gynäk. **126**: 45, 1925)	1925	24	8.70	....	44	No change	0.50	Refractometric, Reizz
Kydd (J. Biol. Chem. **91**: 63, 1931)	1931	..	6.91	....	22	6.21	....	Macro-Kjeldahl
Gram (Acta med. Scandinav. **56**: 106, 1922)	1924	25	....	0.29	57	....	0.55	Gravimetric
Foster (Arch. Int. Med. **34**: 301, 1924)	1924	19	....	0.34	10	....	0.42	Gravimetric (ashed)

* In this table the following abbreviations are used: H = male and female; P = plasma (oxalate or citrate).

nonprotein nitrogen of the serum are determined and the difference multiplied by the constant, 6.25, gives the serum protein. This method requires 2 cc., but preferably 4 cc. (for duplicates) of serum for proper analysis and, at a minimum, forty minutes for a single determination. The interferometric method requires approximately 1 cc. of serum and from eight to ten minutes for an analysis. The last mentioned method, which is also used for the fibrin determination, is far more accurate than any of the others.

Another source of error is the use of plasma, which will give results that are too high because of the presence of fibrinogen, which, in pregnancy, may amount to 1 per cent or more. Furthermore, determination of plasma protein in which coagulation is prevented by means of oxalate, citrate or fluoride, also gives results which are too low, because the electrolyte causes the cells to shrink, thus squeezing out water which dilutes the plasma. This dilution may be great enough to make the serum protein actually higher than the plasma. For proper results, determinations should be made on serum, and the fibrin should be determined separately on plasma. Furthermore, the chief function of the serum protein is in the water exchange in the capillaries, and since fibrin is not concerned in this and has no measurable osmotic pressure, it should not be considered when speaking of serum protein.

The discussion of changes in serum protein in pregnancy, despite their importance in edema and toxemia, is limited in the obstetric textbooks. Thus, DeLee [1] stated:

> The amount of fibrin and fibrinogen increases from the sixth month of pregnancy, and may be one-third greater than usual. This increase of fibrin is probably a conservative act of nature to prevent dangerous loss of blood during labor. Perhaps the hyperinosis causes the thromboses sometimes observed in the veins of the legs and pelvis even before labor.

Williams [2] stated:

> Plass and Matthews, from the study of 314 women, showed that the total plasma protein decreases 9.3 per cent from the beginning of pregnancy to the ninth month, rises at the time of labor, and regains its original figure during the third week of the puerperium. At the same time its several fractions differ in their behavior; the albumin fraction diminishing, the globulin fraction remaining essentially stationary, while the fibrin increases, and attains its greatest height on the third day of the puerperium. Eufinger has approached the problem from a physicochemical point of view, and by means of the refractometer finds that the plasma colloids undergo a characteristic and progressive change toward the large dispersal phase. In other words, coincident with a relative decrease in the total protein, he

1. DeLee, J. B.: Principles and Practice of Obstetrics, ed. 5, Philadelphia, W. B. Saunders Company, 1928.

2. Williams, J. W.: Obstetrics, ed. 6, New York, D. Appleton and Company, 1930.

finds an increase in the euglobulin and fibrinogen fractions. Both of these observations accord with the fact that the specific gravity of the blood is somewhat lowered, while the increase in fibrin may have some connection with the increased sedimentation rate of the blood in the latter part of pregnancy.

Zangemeister [3] stated that the plasma in pregnancy is richer in water, but poorer in protein (a hydroplasmia). Fibrinogen is increased.

Seitz,[4] in the Halban and Seitz series, concluded that there is a definite decrease in serum protein and a slight increase in water.

Denecke [5] concluded that there is a hydroplasmia, but not a hydremia. He also reported an increase in fibrinogen.

Plass,[6] after two separate investigations, concluded that the plasma proteins tend to be diminished, reaching a minimum at the sixth month during pregnancy and the early part of the puerperium. He stated that they are within the normal range at the end of the first week post partum. The fibrin rises during pregnancy to reach a high point shortly after delivery. The relative increase is greater than the absolute change. He pointed out that the existence of dilution of blood and plasma should be considered whenever studies of the blood are done during pregnancy, labor or the puerperium. This work by Plass and Bogert and by Plass and Matthews is the most extensive to date, but is based on analyses of oxalated plasma by the Kjeldahl method in the first report and by Wu's method in the second; the results, therefore, are of value in that they indicate the direction of change.

To summarize, a study of the reports in the literature indicates that the serum protein is decreased during pregnancy and that fibrin is increased, but the actual amount of change and whether or not the decrease in serum protein is primary or secondary to the increase in plasma volume are questions still open to discussion. If determinations of total protein were made, it would be possible to decide whether or not the decrease in the percentage of serum protein is due entirely to the increase in plasma. So far as we know, no one has investigated the changes in the total amount of fibrin in pregnancy.

Mahnert [7] was the only investigator who determined plasma volume and serum protein per hundred cubic centimeters and then calculated the total grams of protein and the grams per kilogram. He stated that in

3. Zangemeister, W.: Ztschr. f. Geburtsh. u. Gynäk. **49**:92, 1903.

4. Seitz, L., quoted in Halban, Joseph, and Seitz, Ludwig: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenburg, 1926, vol. 7, p. 654.

5. Denecke, G., quoted in Hinselmann: Die Eklampsie, Bonn, F. Cohen, 1924, p. 293.

6. (*a*) Plass, E. D., and Bogert, J.: Bull. Johns Hopkins Hosp. **35**:361, 1924; (*b*) Am. J. Obst. & Gynec. **6**:637, 1923; (*c*) Plass, E. D., and Matthews, C. W.: ibid. **12**:346, 1926.

7. Mahnert, A.: Arch. f. Gynäk. **114**:168, 1921.

the nonpregnant woman the maintenance of certain amounts of serum protein per kilogram is one of the fundamental physiologic necessities of the organism, and that, if calculated on a per kilogram basis, the serum protein in the pregnant woman is less than in the nonpregnant woman (0.56 per cent compared with 0.63 per cent), but that if the weight of the fetus and amniotic fluid is deducted, there is an actual increase in pregnancy. This increase in total protein is small, compared with the increase in blood volume.

Serial determinations of plasma volume, serum protein and fibrin were made on the same women at different periods of pregnancy and post partum. A similar study was started on patients at term and continued to eight weeks post partum. The first group is designated series A and the latter as series B. Additional data, not serial, were obtained on other women during pregnancy. All samples of blood were obtained in the morning and, whenever possible, from fasting patients. This is apparently of some importance so far as fibrin is concerned. Earle and Cullen [8] noted that the fibrin clot was much larger if the blood was drawn after meals, with the exception of breakfast. Some unreported work of ours suggests that the ingestion of protein is associated with the increase in the size of the clot, as we have found a measurable increase in the fibrin after a meal containing protein.

METHOD

Plasma volumes were determined with congo red, as previously described. No stasis was used, and the blood was injected under oil into centrifuge tubes. The clot was broken up and the specimen centrifugated within twenty to forty minutes after the venipuncture. A longer or shorter time will affect the proteins, because, as the clot retracts, more water will be forced out of the cells, and the concentration of the proteins will be decreased. Serum protein and fibrin were determined with the interferometer. Approximately 1 cc. of serum and 1 cc. of plasma are required for the determinations. The method is far more accurate and less subject to errors than the refractometric method of Kjeldahl, or the colorimetric method of Wu.

RESULTS

In table 2 are listed variations and averages in serum protein throughout pregnancy and the puerperium. A normal range of from 5 to 8.9 per cent at once indicates the fallacy of studying different groups of patients in pregnancy. The standard deviations and the difference between the means for the various periods of the total cases have been calculated, and the latter figures indicate that the changes in the serum proteins

8. Earle, I., and Cullen, G.: J. Biol. Chem. **83**:539, 1929.

are of no significance. However, the data for series A are of importance because the same patients were studied. These figures indicate a decrease of 6 per cent in pregnancy, and a still further decrease of 2 per cent during the first postpartum week, but then a rapid increase occurs, and at ten to fifteen days the serum proteins show an increase of 7 per cent and are slightly greater than when the patients were first seen. The decrease after delivery is probably due to an overcompensation of plasma volume for the concentration caused by labor, while the continued dilution, coincidental with the negative water balance, may be the result of the shift in water from the tissues (loss of physiologic edema). There is a constant increase after ten days, and at three weeks the

TABLE 2.—*Percentage of Serum Protein: Variations and Averages in Pregnancy and in the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Serum Protein, per Cent	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
5.0-5.4	..	..	..	..	5	..	..	..
5.5-5.9	..	..	1	5	7	2	..	..
6.0-6.4	6	6	17	26	5	9	3	1
6.5-6.9	11	4	6	21	5	13	1	4
7.0-7.4	5	1	2	3	3	5	5	4
7.5-7.9	1	1	..	..	..	1	1	..
8.0-8.4	..	..	..	1	..	1	..	..
8.5-8.9	..	..	..	..	..	..	..	1
Total	23	12	26	56	25	31	10	10
	Mean							
Total cases	6.77 ± 0.06		6.42 ± 0.05	6.51 ± 0.04	6.13 ± 0.09	6.80 ± 0.07		
Standard deviation	0.41		0.40	0.47	0.65	0.57		
Series A	6.76		6.55	6.36	6.11	6.85		
Series B	....		....	6.62	6.52	6.76	6.88	7.26

proteins are at the lower limits of normal. At eight weeks post partum they have increased 14 per cent above the term reading and are within the normal limits.

In table 3 are listed the variations and averages for serum protein calculated on a per kilogram basis. The plasma volume, multiplied by the per cent of serum protein, gave the total amount of circulating protein. This figure, divided by the weight, gave the amount of serum protein per kilogram. The determination of serum protein is an exact measurement, but the plasma volume is only approximate. However, since the determinations were made on the same patients, under similar conditions, the results are of value. Mahnert [7] made similar determinations. His report is based on a study of ten pregnant women on whom serum protein and plasma volume were determined with the refractometer. He stated that in the nonpregnant women the serum protein per kilogram ranged from 3.2 to 6.8 Gm., with an average of 6.3 Gm.,

while in pregnancy the range was from 3.1 to 8.5 Gm., with an average of 5.6 Gm. The maximum amounts were found in the last two months. If corrections are made for the weight of the fetus, placenta and amniotic fluid, there was an actual increase in pregnancy. The difference between the means for the various periods of the total cases has been calculated, and the figures indicate that the changes are of no significance. The amount of serum protein per kilogram is less than that reported by Mahnert;[7] this is due, in all probability, to the following factors: He determined serum protein with the refractometer without filtrate determinations, which gives high readings. He used a refractometric method for determining the plasma volume; the foregoing criticism is also

TABLE 3.—*Serum Protein in Grams per Kilogram of Body Weight: Variations and Averages in Pregnancy and in the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Grams per Kilogram	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
2.0-2.4	5	1	2	3	6	1	..	..
2.5-2.9	5	1	8	16	8	14	2	2
3.0-3.4	7	6	11	22	6	6	2	3
3.5-3.9	5	2	3	12	3	6	3	3
4.0-4.4	2	1	2	2	2	2	1	1
4.5-4.9	..	..	..	..	..	2	2	1
Total	24	11	26	55	25	31	10	10
	Mean							
Total cases	3.13 ± 0.09		3.15 ± 0.07	3.20 ± 0.04	2.99 ± 0.08	3.25 ± 0.08		
Standard deviation	0.62		0.5	0.47	0.59	0.65		
Series A	3.08	3.28	3.09	2.99	2.83	3.50		
Series B	....	....	....	3.34	3.09	3.04	3.88	3.56

applicable to this method. Furthermore, his series is small. Mahnert stated in regard to the nonpregnant women that the maintenance of a certain definite amount of serum protein per kilogram is one of the fundamental physiologic necessities of the organism. The constancy of our figures indicates that this statement is also applicable to the pregnant women. Data on separate patients, which are given in tables 8 and 9, demonstrate this constancy even more clearly.

In table 4 are listed the variations and averages for the percentage of fibrin. In the total series there is an average increase of 20 per cent, which rises still higher during the first postpartum week, and then slowly falls to a figure usually found in early pregnancy. This increase at term is significant. Series A shows an increase of 10 per cent at term, with a slight increase at from ten to fifteen days. Series B shows an increase of 34 per cent in the first postpartum week, and then a gradual decrease to a figure which is still slightly high at eight weeks.

It does not seem to us that the increase during pregnancy is a protective mechanism, as many observers maintain, but it is more likely due to the invasion of the blood by protein elements (chorionic tissue). A high percentage of fibrin is found whenever foreign protein enters

TABLE 4.—*Percentage of Fibrin: Variations and Averages in Pregnancy and in the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
Fibrin, per Cent	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.20-0.29	3	1	4	3	2	2	..	..
0.30-0.39	10	4	8	8	2	12	3	5
0.40-0.49	6	4	8	20	4	9	5	2
0.50-0.59	3	..	2	18	9	6	..	1
0.60-0.69	1	1	2	5	6	2	1	1
0.70-0.79	..	2	1	..	1	..	..	..
0.80-0.90	..	..	1	1	2	..	..	..
Total	23	12	26	55	26	31	9	9
			Mean					
Total cases	0.40 ± 0.01		0.43 ± 0.02	0.48 ± 0.01	0.55 ± 0.02	0.43 ± 0.01		
Standard deviation	0.10		0.15	0.12	0.15	0.10		
Series A	0.40		0.39	0.44	....	0.45		
Series B	....		....	0.47	0.63	0.41	0.42	0.43

TABLE 5.—*Fibrin in Grams per Kilogram of Body Weight: Variations and Averages in Pregnancy and in the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
Grams per Kilogram	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 Weeks
0.10-0.19	16	5	12	13	3	20	4
0.20-0.29	6	4	10	30	15	16	4
0.30-0.39	2	1	3	9	6	3	1
0.40-0.49	..	1	1	2	..	1	..
0.50-0.54	..	..	..	..	1	..	..
Total	24	11	26	54	25	40	9
			Mean				
Total cases	0.187 ± 0.005		0.219 ± 0.01	0.245 ± 0.007	0.269 ± 0.01	0.207 ± 0.008	
Standard deviation	0.064		0.081	0.075	0.081	0.073	
Series A	0.17		0.18	0.21	....	0.23	
Series B	....		....	0.27	0.30	0.20	0.21

the blood stream, as in cancer, infections and nephrosis (infection). Furthermore, the peak of the percentage of fibrin is post partum, when there is not the need for coagulation that there is at term, but when the wound surface (placental area and involution) is at its maximum.

In table 5 are listed the data on the grams of fibrin per kilogram. The calculations are similar to those used in determining the serum pro-

tein per kilogram. The mean figures show an increase of 33 per cent at term in the total cases, and of 23 per cent in series A. This increase at term is significant. There is a still further increase during the first week post partum and then a gradual decrease to a figure which is still higher than those found early in pregnancy.

TABLE 6.—*Average Changes in Serum Protein and Fibrin Calculated from Variations in Total Amount Using the Initial Determination as 100 Per Cent for the Ante Partum Period*

	Serum Protein		Fibrin	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 26 to 35 weeks of gestation:				
Average increase for all patients	18	13.7	18	23.2
Average increase for those showing increase	10	29.3	12	41.7
Average decrease for those showing decrease	4	13.3	3	26.0
No change	4	0	3	0
From 36 to 40 weeks of gestation:				
Average increase for all patients	15	18.3	15	40.0
Average increase for those showing increase	10	29.4	15	40.0
Average decrease for those showing decrease	2	12.0	0	0
No change	3	0	0	0

TABLE 7.—*Average Changes in Serum Protein and Fibrin Calculated from Variations in Total Amount, Using the Last Ante Partum Determination as 100 Per Cent for the Post Partum Period*

	Serum Protein		Fibrin	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 2 to 6 days post partum:				
Average decrease for all patients	25	16.6	25	5.0
Average decrease for those showing decrease	20	21.5	13	28.0
Average increase for those showing increase	1	17.0	9	26.3
No change	4	0	3	0
From 10 to 25 days post partum:				
Average decrease for all patients	41	4.6	40	11.7
Average decrease for those showing decrease	20	20.0	27	32.5
Average increase for those showing increase	12	17.6	8	50.9
No change	9	0	5	0
From 8 to 17 weeks post partum:				
Average decrease for all patients	10	7.4	9	25.7
Average decrease for those showing decrease	5	15.4	6	42.2
Average increase for those showing increase	2	6.5	2	9.5
No change	3	0	1	0

In table 6 are given data on the changes in total amount for serum protein and fibrin. The calculations are as follows: The total amount of serum protein for each period is calculated; the first reading in pregnancy is assumed to be 100 per cent, and all other readings up to and including those at term are divided by this first figure. Thus all the data are converted to per cent changes and can then be compared. Similar calculations were used for the fibrin. There is an average increase of 13.7 per cent in the serum protein at from twenty-six to

TABLE 8.—*Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)* *

Number, Gravida, Color Age	Period of Gestation or Post Partum	Weight	Serum Protein				Plasma Volume	Fibrin			
			Per Cent	Gm. per Kg.	Total Amt., Gm.	Change, per Cent	Change, per Cent	Change, per Cent	Total Amt., Gm.	Per Cent	Gm. per Kg.
			1	2	3	4	5	6	7	8	9
1	13 wks.	46.3	6.79	2.74	127	...	...	...	10.80	0.578	0.23
II	29 wks.	55.9	6.66	3.70	207	163	166	106	11.46	0.369	0.21
W	40 wks.	59.5	6.51	4.22	251	198	206	179	19.28	0.500	0.32
20	12 days	50.4	6.78	4.68	236	94	90	102	19.69	0.566	0.39
2	14 wks.	77.9	6.59	2.48	193	...	...	...	15.00	0.511	0.19
I	30 wks.	81.0	6.88	2.86	232	120	115	166	24.85	0.738	0.31
W	40 wks.	80.9	6.05	2.60	210	109	119	129	19.41	0.558	0.24
23	12 days	73.6	6.79	2.79	205	98	86	69	13.46	0.446	0.18
3	15 wks.	53.0	6.68	3.75	199	...	...	...	10.59	0.356	0.20
I	30 wks.	61.1	6.68	4.06	248	125	125	146	15.44	0.415	0.25
W	40 wks.	63.5	6.42	3.48	221	111	116	122	12.90	0.375	0.20
23	12 days	53.0	7.13	4.23	224	101	91	101	13.02	0.415	0.25
4	14 wks.	92.2	6.87	2.25	207	...	...	...	11.76	0.391	0.13
VII	27 wks.	91.7	6.83	2.74	251	121	122	139	16.33	0.445	0.18
W	40 wks.	87.0	5.83	2.68	233	113	133	112	13.12	0.328	0.15
30	14 days	82.7	6.71	2.43	201	86	75	80	10.52	0.352	0.13
5	12 wks.	53.6	7.01	2.80	150	...	...	...	9.59	0.449	0.18
II	28 wks.	59.5	7.17	3.33	198	132	129	98	9.43	0.342	0.16
W	39 wks.	60.0	6.66	3.32	199	133	140	180	17.22	0.576	0.29
25	14 days	52.5	7.02	4.91	258	130	123	90	15.45	0.420	0.29
6	14 wks.	45.9	6.34	3.05	140	...	...	...	6.96	0.316	0.15
I	27 wks.	54.8	6.08	3.07	168	120	116	130	9.02	0.327	0.16
W	40 wks.	63.5	5.58	2.72	173	124	141	190	13.23	0.426	0.21
19	11 days	56.0	6.49	3.38	189	109	94	116	15.33	0.527	0.27
7	14 wks.	107.2	6.88	2.22	238	...	...	...	14.09	0.408	0.13
VI	30 wks.	112.5	6.37	2.14	241	101	110	77	10.86	0.287	0.10
W	40 wks.	114.6	7.44	2.52	289	121	112	126	17.78	0.458	0.16
31	5 days	100.3	6.79	2.71	272	94	103	117	20.72	0.518	0.21
	13 days	100.4	6.66	3.28	329	114	127	86	15.36	0.311	0.15
8	14 wks.	92.9	7.08	3.29	306	...	...	...	20.34	0.471	0.22
III	28 wks.	103.5	7.12	2.71	281	92	92	95	19.39	0.491	0.19
C	40 wks.	106.9	6.89	2.72	296	97	100	106	21.51	0.500	0.20
30	11 days	100.0	....	....	...	...	85	...	.....	.....	....
9	14 wks.	50.0	6.50	3.26	163	...	...	...	5.10	0.204	0.10
I	29 wks.	58.8	6.13	3.30	194	119	127	139	7.10	0.224	0.12
C	40 wks.	60.0	6.31	3.40	204	125	129	185	9.41	0.291	0.16
21	3 days	55.8	6.12	3.33	186	91	94	102	9.57	0.314	0.17
	12 days	52.5	6.80	3.83	201	99	92	69	6.52	0.220	0.12
10	20 wks.	71.8	6.75	3.01	216	...	...	...	11.92	0.372	0.17
I	36 wks.	75.5	6.30	3.01	227	105	113	169	20.16	0.560	0.27
W	3 days	70.3	5.43	2.46	173	76	88	43	8.68	0.273	0.12
26											
11	15 wks.	67.2	6.24	2.20	215	...	...	...	13.31	0.387	0.20
I	28 wks.	73.8	6.20	2.95	218	101	102	124	16.56	0.471	0.22
W	39 wks.	76.5	6.22	2.86	219	102	102	106	14.38	0.409	0.19
22	12 days	68.1	6.95	3.36	229	105	94	141	20.22	0.613	0.30
12	9 wks.	61.3	7.40	3.72	228	...	...	...	13.69	0.445	0.22
I	27 wks.	80.0	6.36	3.26	261	114	133	102	14.03	0.342	0.18
C	40 wks.	86.3	6.42	2.33	201	88	102	110	15.12	0.482	0.18
28	11 days	75.6	7.32	2.98	225	112	97	111	16.79	0.546	0.22
13	11 wks.	68.1	6.76	3.55	242	...	...	...	8.23	0.230	0.12
VIII	29 wks.	75.4	6.33	3.20	241	100	106	122	10.06	0.264	0.13
C	40 wks.	71.5	6.02	2.99	214	88	99	132	10.84	0.305	0.15
37	11 days	65.6	6.73	3.38	222	104	93	170	18.47	0.560	0.28
22	16 wks.	55.7	6.59	3.55	198	...	...	...	6.45	0.215	0.12
II	28 wks.	64.3	6.30	2.80	180	91	95	171	11.03	0.386	0.17
W	40 wks.	67.5	6.07	....	...	...	...	...	.....	0.420	....
24	12 days	60.8	6.43	2.81	171	...	...	...	8.88	0.336	0.15

* In this table, W indicates white race; C, colored race.

thirty-five weeks, and an average increase of 29.3 per cent in ten of the eighteen patients studied. Four showed a decrease of 13.3 per cent and four no appreciable change (5 per cent or less). At term the average increase for the serum protein was 18.3 per cent, and in ten of the fifteen patients studied, 29.4 per cent. Two showed an average

TABLE 9.—*Data on Patients Followed from Term to Eight Weeks Post Partum (Series B)* *

Number, Gravida, Color, Age	Period of Gestation or Post Partum	Weight	Serum Protein				Plasma Volume	Fibrin			
			Per Cent	Gm. per Kg.	Total Amt., Gm.	Change, per Cent	Change, per Cent	Change, per Cent	Total Amt., Gm.	Per Cent	Gm. per Kg.
			1	2	3	4	5	6	7	8	9
31	39 wks.	67.0	5.93	3.53	237	...	...	...	20.36	0.509	0.30
I	12 days	56.5	6.14	2.78	157	66	64	50	10.25	0.400	0.18
C	8 wks.	53.6	....	....	...	...	74	...	.....	.....	....
15											
32	40 wks.	65.0	6.12	3.14	204	...	...	...	13.50	0.405	0.21
I	3 days	58.0	5.60	2.48	144	71	77	103	13.84	0.537	0.24
W	12 days	55.5	6.38	3.15	175	86	82	81	10.94	0.399	0.20
27	8 wks.	60.5	6.80	3.06	185	91	82	66	8.86	0.325	0.15
33	40 wks.	103.4	6.74	2.52	261	...	...	...	13.38	0.345	0.13
II	3 days	90.0	6.98	2.94	265	102	98	181	24.24	0.638	0.27
W	19 days	87.5	6.33	2.50	219	84	89	100	13.33	0.386	0.15
29	9 wks.	89.2	6.94	3.14	280	107	104	107	14.29	0.354	0.16
34	40 wks.	72.2	6.58	3.28	237	...	...	...	20.59	0.572	0.29
I	5 days	63.1	5.88	2.42	153	65	78	85	17.50	0.674	0.28
C	8 wks.	64.5	7.28	3.58	231	97	88	55	11.28	0.356	0.17
25											
35	36 wks.	68.1	6.70	3.10	211	...	...	...	13.40	0.425	0.20
II	11 days	61.5	6.55	2.96	182	86	88	78	10.51	0.378	0.17
W	8 wks.	58.6	6.96	3.16	185	88	84	103	13.75	0.518	0.23
24											
36	40 wks.	68.4	8.40	3.80	266	...	...	...	20.86	0.660	0.30
I	3 days	63.0	7.40	4.08	257	97	110	76	15.86	0.456	0.25
C	12 days	56.8	8.30	3.98	226	85	86	67	13.91	0.511	0.24
25	8 wks.	54.5	8.95	5.19	283	106	100	65	13.60	0.430	0.25
37	38 wks.	82.0	6.35	3.78	310	...	...	...	14.74	0.302	0.18
I	12 days	73.0	6.72	2.68	196	63	60	69	10.10	0.346	0.14
W	8 wks.	75.0	7.21	4.00	300	97	85	112	16.54	0.398	0.22
30											
39	39 wks.	67.5	6.40	3.34	208	...	...	...	16.04	0.493	0.26
I	11 days	51.9	6.48	2.70	140	67	67	61	9.84	0.454	0.19
W	17 wks.	50.0	6.94	2.64	132	63	59	...	.....	.....	....
17											
40	40 wks.	54.0	6.64	3.61	195	...	...	...	26.70	0.910	0.49
III	3 days	48.2	6.60	3.86	186	95	96	96	25.69	0.910	0.53
C	25 days	46.8	7.12	4.44	208	107	100	49	13.02	0.445	0.28
28	8 wks.	47.2	7.14	3.64	172	88	82	60	16.01	0.665	0.34
43	38 wks.	72.2	6.33	3.25	235	...	...	...	25.01	0.674	0.35
I	5 days	63.5	6.70	2.77	176	75	71	57	14.14	0.537	0.22
C	19 days	62.2	7.19	4.71	293	125	110	72	18.02	0.442	0.29
17	8 wks.	61.9	7.09	3.63	225	96	86	53	13.14	0.414	0.21

* In this table, W indicates white race; C, colored race.

decrease of 12 per cent, and two showed no change. There was a marked increase in fibrin at from twenty-six to thirty-five weeks, but the most striking point was that all fifteen patients showed an average increase of 40 per cent at term.

In table 7 are given data on the changes in total amount after delivery. The calculations are similar, except that the reading at term

is assumed to be 100 per cent and all subsequent figures are divided by it. There is a definite decrease in serum protein after delivery, which is most marked in the first week. The fibrin shows a constantly increasing diminution, reaching a maximum decrease of 25.7 per cent at eight weeks, thus confirming the statement that there is an increase during pregnancy.

Table 8 lists essential data on the separate patients comprising series A. During pregnancy only one patient showed an increase of 8 per cent in serum protein at term, although at thirty weeks' gestation there had been a decrease of 7 per cent. All of the others had decreases, varying from 0.3 to 15 per cent. The average decrease was 7 per cent. There are variations of considerable magnitude in the grams of protein per kilogram, but the fact that there is some relatively constant figure for each patient indicates, we believe, that there is an optimum amount of serum protein which the body tends to keep constant. The figures for percentage of fibrin are very irregular, and although most of the patients showed some increase at term, the greatest increase was post partum. The total amounts of fibrin and also the grams per kilogram showed marked increases in pregnancy in all cases. The change in eight cases amounted to 50 per cent or more.

Table 9 lists essential data on the separate patients comprising series B. The increase of serum protein to within normal limits at eight weeks is evident. The values have not returned to normal at the end of the first week post partum, as stated by Plass and Bogert,[6a] if studied individually or collectively. The percentage of fibrin and the number of grams per kilogram were variable, but were decidedly lower at eight weeks post partum. The decreases in total fibrin were just as great post partum as the increase had been during pregnancy in series A.

COMMENT

It is difficult to understand why the percentage of serum protein should decrease in pregnancy. Our study of the separate patients shows that the decrease is not nearly as great as heretofore believed. In fact, some might consider the change of no significance, but the decrease in most of the patients is much more than the error of the method, and, as we have demonstrated by bi-hourly studies, the percentage of serum protein is a constant entity; therefore, the decrease is significant.

The explanation heretofore given that the decrease in the percentage of serum protein is due to the watery dilution of the blood is untenable with the definite increase in total serum protein. One obvious explanation is that the body attempts to keep the serum protein constant as the plasma volume increases, and that it cannot compensate any closer than it does. However, we are finding changes in many of the impor-

tant constituents studied, and although they are not of the same magnitude, the direction of the change is, as a rule, the same. Therefore, it seems to us that there is a definite plan in the changes which, if solved, will throw considerable light on metabolism of water, on edema and on renal function both in health and in disease.

The changes in fibrin in pregnancy may be due to the stimulus produced by the constant breaking off of chorionic villi (deportation of Veit [9]). Mills [10] has demonstrated that in vivo injections of tissue extract or extracellular fluid, which is comparable to the breaking off of a villus, at which time a minute amount of extracellular fluid is set free, produces a definite increase in fibrin. Figures for fibrin are especially high in eclampsia, in which the deportation, supposedly, may be at its maximum. The facts that fibrin is also markedly increased in cancer and in infection and that our figures are greatest after delivery make the theory improbable that the increase is a protective one for coagulation of the blood.

Our work also demonstrates the unreliability, at least, of chemical data obtained from various groups of women during pregnancy, especially if the substance being studied has a wide normal range.

CONCLUSIONS

The normal figures for serum protein and fibrin reported in the literature for both nonpregnant and pregnant women are based on a relatively small number of determinations, and the data on the latter are especially confusing, either because of the methods used or because serial determinations on the same women were not made.

Determinations of serum protein, fibrin and plasma volume were made on various patients for the different periods of pregnancy and the puerperium. The results were studied statistically, and the following conclusions were made:

1. The changes in percentage of serum protein and in amount of serum protein per kilogram of body weight are of no significance.

2. The changes in percentage of fibrin and in amount of fibrin per kilogram of body weight are significant. At term the former has increased 20 per cent and the latter 30 per cent.

A similar study in which the observations were made on the same women indicates that:

1. The serum proteins at term are from 0.3 to 15 per cent—average 7 per cent—below those of the first trimester. There is a still further

9. Veit, J.: Die Verschleppung der Chorionzotten, Wiesbaden, J. F. Bergmann, 1905.

10. Mills, C., and Guest, G.: Am. J. Physiol. **57**:395, 1921.

decrease the first few days post partum and then a slow rise, reaching a normal figure at about eight weeks post partum.

2. The amount of serum protein per kilogram remains rather constant during pregnancy, ranging from 2.5 to 3.5 Gm., with an average that is approximately 3.0 Gm. per kilogram.

3. Determinations of the total amount of serum protein indicate that there is an average increase of 14 per cent at from twenty-six to thirty-five weeks, and an increase of 18 per cent at term. The figures post partum are extremely variable, with the major portion of the patients showing a decrease which, after the first week, is almost negligible.

4. Figures for the percentage of fibrin show marked variations, but there is an average increase at term of 10 per cent. At eight weeks post partum the figures are still above normal.

5. The grams of fibrin per kilogram show a more marked increase during pregnancy, reaching a maximum during the first week post partum and then slowly decreasing, but at eight weeks the figures are still above normal.

6. Determinations of the total amount of fibrin indicate an average increase of 23 per cent at from twenty-six to thirty-five weeks, and an increase of 40 per cent at term. During the first week post partum there is a slight decrease amounting to 5 per cent, but at eight weeks the average decrease is 26 per cent, thus furnishing additional evidence that there had been an increase in pregnancy.

7. The decrease in serum protein, even if the loss were all albumin, is insufficient in itself to cause physiologic edema. Changes in the osmotic pressure, surface tension and base-binding power of the proteins out of proportion to the decrease seem to indicate that there are intrinsic alterations in the proteins themselves.

A COMPARISON OF THE DEVELOPMENT OF THE SPECIFIC NODULE OF SILICOSIS AND OF TUBERCULOSIS

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The earliest historians dealing with mining and the hazards of the industry as they affected the health of the miner have recognized a relationship between the various types of dust and the production of disease. They knew of corrosive and noncorrosive types of dust, both of which produced disability, the former causing such serious injury to the lung that death ensued. Because the sickness resembled what is now called tuberculosis, the term "dust phthisis" came into use. Many patients suffering from dust phthisis became emaciated, coughed productively, had fever and died. It has been reported that in the sixteenth century in the mining communities of the Carpathian Mountains many women could be found who had been widowed time after time by miner's phthisis. The exact relationship between the corrosive and noncorrosive dusts was slow in being established. Finally, however, in the early part of the nineteenth century, Alison, professor of medicine at Edinburgh, established the association between dust phthisis and tuberculosis, that is, between dust phthisis and true phthisis. It was not dust itself that was responsible for the "ulceratio" of Celsus but a secondary complication. The "corrosive dust" noted by Agricola in the sixteenth century and by Ramazzini in the eighteenth century became the "tuberculosis" of Alison. Fifty years ago, the bacillus of tuberculosis was discovered and added a final confirmation to Alison's work, and less than twenty years ago it was shown that the only dust of importance in the production of dust phthisis is silica. As a result, the term "silicosis" is being used to cover all forms of harmful pneumonoconiosis.

The relationship between the noncorrosive and the corrosive forms of dusts was further emphasized when it was shown that one condition

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was uncomplicated by infective agents and produced "simple silicosis," whereas the other operated in association with infection and produced what is now termed "infective silicosis." The infection most commonly acting as a complication was proved to be set up by the bacillus of tuberculosis, and the degree of responsibility of each as an etiologic factor was expressed by the terms employed: "silicotuberculosis" and "tuberculosilicosis." These terms are intended to indicate which of the two was the primary and which the secondary or complicating factor.

The pathologic study of the lesions in simple silicosis further emphasizes the bond of similarity existing between the two diseases. Silica arrested in the lung produces nodules resembling those characteristically formed by the arrest of Mycobacterium tuberculosis. Its phthisis-producing capability is dependent on its relative inertness and insolubility. It is thus relatively indestructible and can remain indefinitely impounded within the lung. It is too inert seriously to injure the phagocyte that ingests it, and too inert to cause an exudative reaction that might facilitate its removal; yet, being slightly soluble in tissue juices and slightly irritant, it is able to encourage proliferation over a long period of time. Because silica is relatively inert, the injury produced depends on the number of particles arrested in the lung and on their intracellular reactions. This in turn depends on the size of the particles, which in order to permit of phagocytosis must be approximately that of a micro-organism.

Similarly, the reaction to the bacillus of tuberculosis depends on its relative inertness and indestructible characteristics. It is protected against destruction by its waxy envelop; it does not immediately destroy its cellular host but rather lives, grows and multiplies within the phagocytic cell; it does not immediately produce a highly exudative reaction unless it is present in great numbers or unless its host has been sensitized to it. Unlike silica, it is dependent neither on size nor on number for its effect. Silica must be in particles of less than 10 microns, and there must be as many as 10,000,000 particles in each cubic foot of air if characteristic nodules in the lung are to result from inhalation. If only few, the bacilli may cause nodules, and they are always of a size that is readily phagocytosed. They are alive and multiply, and the resulting injury is progressive. Silica is inorganic, incapable of multiplication, and the resulting injury may be self-limited.

METHOD OF STUDY

In order to observe and compare the reactions in tissue that resulted from invasion of these common and frequently associated irritants, we injected through a cannula introduced into the trachea, suspensions of particles of silica of suitable size and number in a series of normal rabbits. At the same time, we injected the same amount of a suspension of virulent bacilli of tuberculosis of avian type (Mycobacterium avium) into an equal number of normal rabbits. These animals

were killed in pairs at equal intervals of from five hours to four weeks. The resulting lesions were compared for gross and microscopic similarities and differences. The limit of four weeks for the duration of the experiment was chosen because we knew that under the conditions of the experiment the reactions of silica are completed within that length of time, and because we did not wish to be confused by the domination of inflammatory reactions consequent on reinfection of the tuberculous animals. It was obvious that the advantage in the method depended on the speed of the reaction induced when silica was used and on the certainty of producing an infection when employing the bacilli of tuberculosis. It was equally obvious that in the case of silica the disadvantage consisted in the added ease of its removal. Animals that were given injections of silica needed to be well under the influence of the anesthetic; if they were not, they rid their lungs of all particles, and a lesion did not result.

RESULTS

Reactions Due to Bacilli of Tuberculosis.—The first reaction of the lung to the introduction of the organism seemed to be entirely nonspecific and in every way resembled that resulting from the introduction of such inert substances as graphite. The following occurred: a mild degree of atelectasis and an associated inflammation characterized by hyperemia, exudation of serum and an inrush of polymorphonuclear cells with the formation of an exudate within the bronchi, the bronchioles and the finest of their subdivisions. The wandering of polymorphonuclear cells could be determined, and their passage from the parenchyma into the bronchial lumen demonstrated. Also as a nonspecific reaction of defense, phagocytosis took place and made the polymorphonuclear cells and the alveolar phagocytes conspicuous. It is certain that this mechanism is brought into operation almost instantly, and that the mononuclear cell or alveolar phagocyte is the more active of the two, although the polymorphonuclear cell exhibits phagocytosis and is present in far greater numbers. The next nonspecific defense mechanism consisted in the removal of the bacilli from the lung; this is accomplished by two means: The bronchial mechanism is effective and is made possible by the action of ciliated cells and a sensitivity of the mucosa resulting in the production of cough. The lymphatic system is effective as a drainage mechanism, as evidenced by the presence of bacilli within the regional nodes and even in the abdominal viscera within as brief a period of time as one hour. The effectiveness of the lymphatic system is made possible by the ability of the actively functioning phagocyte to wander throughout the parenchyma to those situations in which lymphatic vessels normally exist. Thence, these bacteria-laden cells are hurried outward toward the pleura or toward the hilus on their way to join the main lymphatic trunks. If it were possible for these mechanisms of defense to remove all bacilli and their products, no lesion would result. A lesion is made possible by retention within the lung of bacilli which have the following characteristics: They have a protective envelop to defend them against injury; they can live a

parasitic life; they grow and multiply; they are retained within the cytoplasm of the phagocytic cell; they destroy the cell; they escape, become extracellular and are phagocytosed again, and the cells containing them move from situation to situation. Within five hours, aggregations of phagocytic cells could be found filling the lumens of small bronchioles, and crowding together within alveolar sacs. They were potential tubercles. These aggregations appeared in that tissue, rich in lymphatic structures, which surrounds bronchi and vessels. The cells composing such aggregations appeared more actively phagocytic than those in adjacent interstitial tissue farther removed from a supply of oxygen. Such potential tubercles did not appear within the lymph follicles peripheral to large bronchi unless the bacilli had been introduced intravenously.

Within twenty-four hours the degree of pneumonic consolidation increased, and definite evidence of degeneration and fragmentation of polymorphonuclear cells appeared. Mononuclear cells became more and more numerous, and the large vacuolated phagocytes actively ingested not only large numbers of bacilli but also nuclear fragments or even whole polymorphonuclear cells. Along with evidence of necrosis, fat droplets were becoming conspicuous in the vacuolated cells and in those that were undergoing fragmentation. Mitotic figures appeared and bore testimony to the hyperplasia of mononuclear elements of fixed tissue origin.

After two days, although the large number of polymorphonuclear cells indicated that an exudative inflammation still existed, within the affected parts lesions appeared which were more discrete, more definitely spherical, peribronchial and increasingly mononuclear in type. Mitosis of nuclei, fat droplets in the cytoplasm of phagocytic cells and necrosis were much more conspicuous. When necrosis was most noticeable, and in those places in which the alveolar spaces were crowded with actively functioning mononuclear phagocytes, cells resembling fibroblasts enveloped spherical collections and produced the appearance of miliary tubercles set down in hyperplastic mononuclear pneumonic tissue. The central cells of the aggregation were mononuclear phagocytes, and an occasional degenerating polymorphonuclear cell was seen. There was a tendency to a central axial and a peripheral concentric arrangement of cells within the envelop of fibrils. Indistinct laminae were observable, the cells composing their layers being connected by the interlacing of their protoplasmic projections.

Within a week, the mononuclear cells had taken on the appearance and staining characteristics of mature epithelioid cells. Developing from simple inflammation characterized by a preponderance of polymorphonuclear cells, there had evolved a more specific inflammation characterized by a preponderance of mononuclear cells which were

recognizable as the epithelioid cell of the histologic tubercle of tuberculosis. The arrangement of cells in roughly spherical groupings with concentric laminae, their peripheral investment by fibroblasts and the enveloping zone of mononuclear cells of the lymphocytic order were characteristically and unmistakably those of tuberculosis. The forma-

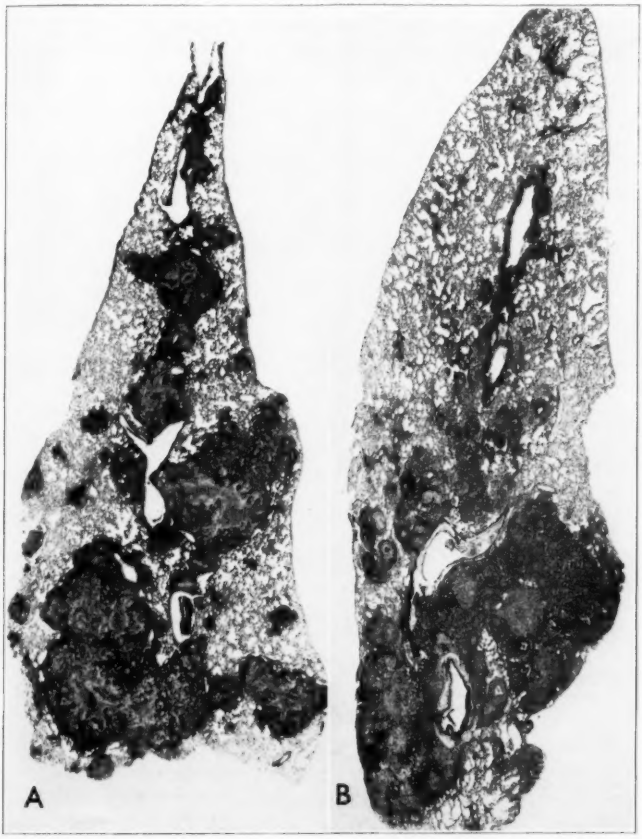

Fig. 1.—*A*, massive and discrete lesions of experimental tuberculosis. The size of the lesion corresponds to the size of the bronchus to which it is adjacent. The subpleural lesions are small and discrete. *B*, lesions of experimental silicosis. The size, situation and physical characteristics of the lesions produce a close resemblance to lesions of tuberculosis. The lesions of tuberculosis and of silicosis are found in tissue rich in lymphatics and result from the cellular reactions induced by impounded Mycobacterium tuberculosis and particles of silica respectively.

tion of the tubercle occurred in association with the development of interstitial pneumonia. The tubercle might be isolated, but it was

usually seen as a discrete unit incorporated within a massive process of mononuclear pneumonitis. Within two weeks, however, gross evidence of the formation of tubercles occurred as isolated miliary tubercles distant from the massive tuberculous pneumonia that included all the structures of the lung adjacent to the large bronchi. The miliary tubercles were more adequately invested by fibroblasts, collagen appeared, and argyrophyl fibers penetrated into the center of the nodules, forming a fine interlacing meshwork. At this time, phenomena of obliteration appeared, and with them central necrosis could be observed. Caseation, excavation and ulceration developed, and in one

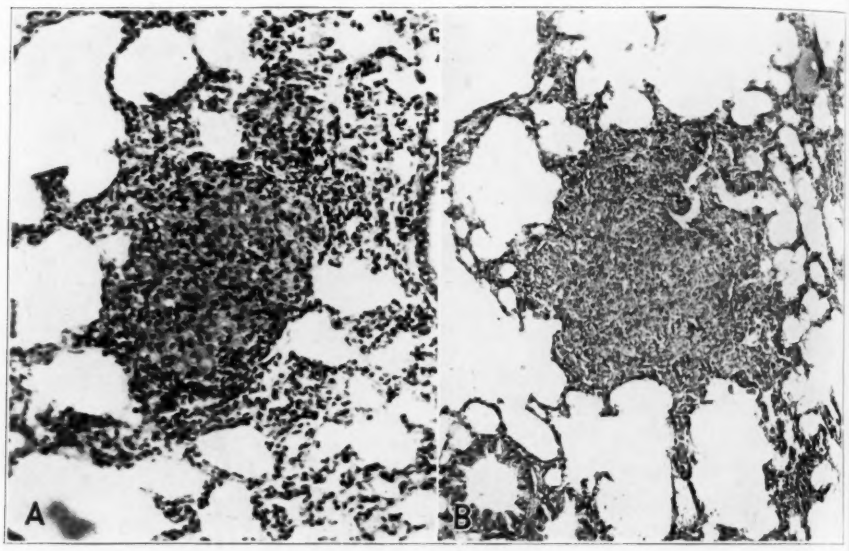

Fig. 2.—*A*, young, discrete peribronchial cellular tubercle of tuberculosis. *B*, young, discrete peribronchial cellular nodule of silicosis.

instance rupture of a tubercle into the lumen of its adjacent bronchus had already taken place. Within four weeks, caseous massive pneumonia created a central core of consolidation extending along the course of the bronchi, diminishing in size from hilus to periphery. Its physical characteristics of size and situation were determined by the anatomic distribution of lymphatic structures. It included within itself many discrete, encapsulated tubercles, many evidences of caseation and many of ulceration. About the periphery were numerous miliary tubercles of classic conformation. Giant cells had made their appearance, collagenous envelops were more conspicuous, fibroblasts

and lymphocytes were included in the spaces between interlacing fibrils, wisps of collagen penetrated into the central portion of the tubercle, and a closely woven network of argyrophil fibrils composed the reticulum of the nodule.

In the lungs of animals which received an intravenous injection of virulent bacilli of tuberculosis of avian type, the miliary tubercles developed without obvious exudative inflammation. The earliest tubercles observed were minute spherical aggregations of mononuclear

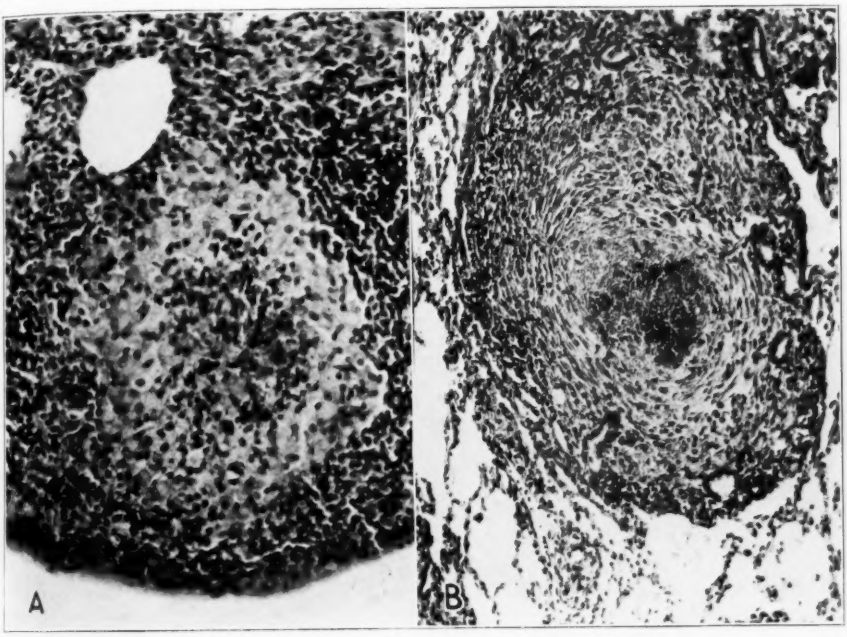

Fig. 3.—*A*, mature tubercle which developed three weeks following intratracheal inoculation of Mycobacterium tuberculosis, showing a central area of necrosis surrounded by indistinct layers of epithelioid cells and a peripheral wall of lymphocytes. *B*, silicotic nodule which developed three weeks following an intratracheal injection of silica. It has a similar central necrotic area, but the mononuclear phagocytic cells are more definitely arranged in concentric laminae. The formation of fibrous tissue is advancing about the periphery, and there is a narrow band of lymphocytes encircling the nodule.

cells recognizable as the typical epithelioid cells of the tubercle, surrounded by small mononuclear cells of lymphocytic type. Later, when infection had spread from the original foci, the tubercles became situated in lymphatic tissues approximating the bronchi and vessels, after

which the lesions passed through the same physical and cellular changes as those formed following intratracheal introduction of organisms. Obviously, the limited numbers of organisms introduced by way of the blood created an inconspicuous inflammatory response. The proliferative reactions with the creation of tubercle seemed to have appeared without any preceding exudative phenomena.

The Silicotic Nodule.—After the introduction of particulate silica into the lung, the inflammatory reactions are immediate, acute and

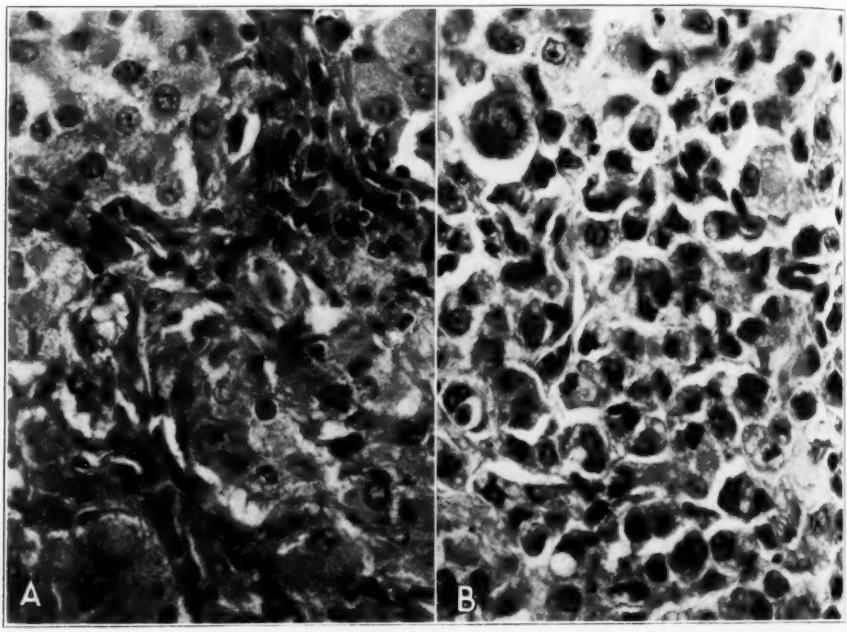

Fig. 4.—*A*, mononuclear phagocytic cells (epithelioid cells) from the mature tubercle of tuberculosis. Giant cells and mitotic figures are not seen in the illustration. *B*, mononuclear phagocytic cells (histiocytes) from the mature nodule of silicosis. Giant cells were never observed. Mitotic figures were occasionally found.

extensive. The pneumonitis is characterized by the exudation of a large amount of serum, an inrush of multitudes of polymorphonuclear cells and the formation of massive consolidation, largest at the hilus and ending as small focal peribronchial or peribronchiolar consolidations. The process of early phagocytosis by mononuclear cells started promptly, but was inconspicuous because of the preponderating inflammatory reactions.

The removal of the silica by both bronchial and lymphatic routes was promptly begun and rapidly accomplished. Many animals had completely rid themselves of silica within from four to eight hours. Many others were free from lesions a month after the injection. Silica must be arrested within the lung and must become fixed there before lesions can develop. Within three days, recognizable spherical aggregations of mononuclear phagocytes could be found. These were incorporated within the massive consolidations, or were discrete and situated mainly in tissue approximating the bronchi or the subdivisions of bronchi. By aid of the polarizing microscope, the particles of silica could be identified. They were found only where hyperplasia occurred and only where mononuclear phagocytes could be identified. In only a single instance was phagocytosis of silica observed in a polymorphonuclear cell. After three days the region of exudative pneumonitis decreased; the serum and erythrocytes disappeared from the parenchyma, and the polymorphonuclear cells became fragmented and decreased in number. There seemed to be a distinct stimulation of monocytes, the number of which rapidly increased.

Within a week monocytes were the most conspicuous cells in the massive consolidation, and the discrete lesions were composed of cells so arranged and so similar morphologically to epithelioid cells as to make the nodule indistinguishable from the young tubercle caused by the bacillus of tuberculosis.

During the second week a central necrotic zone developed in the nodule. This zone contained both free and phagocytosed particles of silica, peripheral concentric layers of mononuclear phagocytes containing phagocytosed particles, and an outer zone rich in fibroblasts lying in the meshwork of interlacing collagenous fibers. About the whole irregularly spherical nodule was a zone of lymphocytes which demarcated the nodule from the adjacent normal parenchyma. Fibroblasts and collagen passed from the periphery into the nodule, and a dense reticulum was demonstrable by differential staining methods. The transition of the mononuclear phagocyte into a cell similar to—if not identical with—the fibroblast could be observed in the outer layers of the mononuclear laminations. Fat droplets were conspicuous in properly stained sections; they were most conspicuous in the necrotic center but were also seen in the cytoplasm of the phagocytic monocytes. Ulceration into the bronchial or vascular structures did not occur within four weeks, but in the animals observed for two months it occurred not infrequently and was the cause of death of many animals. In one animal only was there replacement of the necrotic center by calcium salts. This animal was examined three weeks after receiving the injection. By the fourth week, there were increasing fibrosis, a heavier investment of the nodule by collagenous fibers, deeper penetration of

the nodule by collagen and a meshwork of dense and coarse argyrophil fibers within the nodule.

COMMENT

When the organisms of tuberculosis are introduced intratracheally into some animals, and when particles of silica are similarly introduced into others, the reactions leading to production of the specific nodules in both groups are the result of certain factors which the injected substances have in common. Each substance is relatively inert and relatively impervious to injury or destruction by the tissues; each has the ability to become arrested within the lung and thereafter to stimulate hyperplasia of mononuclear cells. In each instance, the lesion is found in regions rich in lymphatic tissue. The resulting specific lesion in each case is preceded by an exudative inflammation, more intense in the case of silica than in that of the organism of tuberculosis.

The ability of the living bacillus to grow and increase in number causes a provocative response which is progressive. The inability of silica to increase in number of particles and the progressive removal of the initial dosage cause a gradual decrease in the number and size of the lesions.

Phagocytosis of bacilli of tuberculosis by polymorphonuclear cells is much more frequent than phagocytosis of particles of silica. The most actively phagocytic cell in either case is the alveolar phagocyte. Both irritants stimulate hyperplasia of mononuclear cells which ultimately assume an epithelioid appearance, and the nodules formed are constructed of cells of this type. No significant differences could be discovered between the epithelioid cell of the tubercle and the mononuclear phagocyte of the silicotic nodule.

The tuberculous nodule retained its cellular integrity longer than the silicotic nodule; it developed a necrotic center more slowly and much more slowly became invested by collagen. The reticulum of the tuberculous nodule was slower in development and was composed of finer interlacing fibers. The tendency to the development of caseous, massive pneumonia and to a spread by ulceration into adjoining bronchi or blood vessels was much more evident in tuberculosis than in silicosis.

Both types of nodules were avascular and similarly constructed; they had a similar distribution of fat droplets and a similar distribution of bacilli or particles within the nodules.

Both lesions appeared to be the reaction of the reticulo-endothelial system to irritative substances capable of initiating comparable inflammatory phenomena.

SUMMARY AND CONCLUSIONS

In order to obtain material for a comparative study of the respective morphologic reactions provoked in the lung by particulate silica and by bacilli of tuberculosis, intratracheal injections were given to two series

of rabbits. The animals were killed at intervals of from four hours to four weeks after receiving the respective inoculums, and the course and character of the resultant cellular response were studied histologically. The results obtained appear to warrant the following conclusions:

1. The character of the cellular response to the irritative influences of particulate silica and to bacilli of tuberculosis is essentially the same; both promote the formation of characteristic tubercles.

2. The properties of the provocative agent responsible for the production of the silicotic tubercle preclude the formation of a structure characterized by continuous progression. This contrasts markedly with that formed as a consequence of the injection of bacilli of tuberculosis, which is usually of a progressive, destructive nature.

3. The similarity of the structural unit or tubercle invoked experimentally in response to particles of silica and to bacilli of tuberculosis is so striking as to make their certain differential identification impossible by ordinary morphologic criteria.

4. Although the pathologic characteristics of the two processes are practically identical during the early period of cellular progression, significant structural differences become evident as the duration of the diseases is extended.

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LIPOIDS AND LIPOID DISEASES

II. XANTHOMATOSIS (SCHÜLLER-CHRISTIAN'S TYPE)

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The clinical syndrome known variously as Schüller-Christian's disease, Christian's syndrome, xanthomatosis of the skeletal type and dysostosis hypophysaria and also described as "defects in membranous bones, exophthalmos and diabetes insipidus" was first described by Hand [1] in 1893. Hand presented the case of a 3 year old boy with exophthalmos and polyuria in whom autopsy revealed a soft, movable yellow spot about the size of a five cent piece, involving the entire thickness of the skull in the right parietal region. In 1916, Schüller [2] reported two cases, one in a boy of 16 with dystrophia adiposogenitalis, exophthalmos and marked cranial defects and the other in a girl of 4 years with polyuria, exophthalmos and defects of the skull. Schüller felt that both cases were examples of skeletal defects secondary to disease of the hypophysis. Christian,[3] in 1919, reported a case of defects in the membranous bones, exophthalmos and diabetes insipidus, called attention to Schüller's case and, like Schüller, maintained that the syndrome was due to a pituitary disturbance. During the ensuing several years other examples of this syndrome were presented. Of particular interest is the report of Thompson, Keegan and Dunn [4] of a case with complete postmortem examination. They concluded that the disease was not a pituitary dysfunction but was due to infection and that the symptom of polyuria, in accordance with the work of Bailey and Bremer [5] and Curtis,[6] was due to involvement of the hypothalmic region,

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From the Department of Pediatrics and Infectious Diseases, University of Michigan.

Read before the Columbus Academy of Medicine, Columbus, Ohio, Nov. 7, 1932.

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in this case by pressure changes secondary to the cranial defects. Denzer,[7] in 1926, pointed out that in view of the chronological development of the syndrome in his case, the bone defects are primary and exophthalmos and diabetes insipidus are incidental and not essential lesions.

The most important contribution to the problem of Schüller-Christian's disease was made by Rowland[8] in 1928. He reviewed the literature, presented two cases of his own and showed that Schüller-Christian's disease is a special form of xanthomatosis, probably due to a primary disturbance of lipoid metabolism closely related to essential xanthomatosis, Niemann-Pick's disease and Gaucher's disease. Epstein and Lorenz[9] showed that there is a tendency to a specificity of lipoid deposition in this group of conditions, the preponderant lipoid varying with the disease. In Schüller-Christian's disease the lesions contain considerable cholesterol. In Niemann-Pick's disease phosphatides predominate, and in the lesions of Gaucher's disease cerebrosides are in the ascendancy.

The etiology of Schüller-Christian's disease is unknown. The relationship of the condition to diabetes insipidus and the constitutional evidence of pituitary dysfunction suggest a possible endocrine dyscrasia. However, these factors are probably secondary to defects in the skull; it is unlikely that endocrine dysfunction is of etiologic importance. Infection has been shown to have a chronological connection with the disease, but as is true of the majority of childhood diseases, it is nearly always possible to obtain a history of a preceding infection. Trauma seems to play a part in the etiology, since a history of trauma at the site of defects in the skull previous to their development is common, and it is true that in essential xanthomatosis the cutaneous lesions develop at points subjected to the most trauma. There is phagocytosis of lipoids by the cells of the reticulo-endothelial system. Whether this is due to an avidity of the cells for lipoids or is a compensatory mechanism resulting from a failure of proper fat metabolism is problematic. Rowland expressed the belief that there is a constitutional anomaly of lipoid metabolism, and that this constitutional tendency plus various external factors may produce the disease.

Pathologically, Schüller-Christian's disease is characterized by yellowish, rubbery lesions arising from the dura, extending for varying distances through the tables of the skull and eventually occupying its

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entire thickness. In the long bones, similar lesions are found extending inward from the periosteum. Scattered throughout the bone marrow and viscera are small yellowish areas of the same quality, microscopically, as the bone lesions. Histologically, these lesions consist, early in their development, of a mass of lipoid-laden histiocytes known as xanthoma or foam cells. As the process grows older there is connective tissue proliferation with fibrotic replacement of the xanthoma cells. This fibrotic element reaches the clinical horizon most notably in the lungs, since pulmonary fibrosis is marked and is commonly the cause of death in this condition.

The onset of the disease is insidious. The patient is most often brought to the physician complaining of exophthalmos, excessive thirst and polyuria, failure to gain weight, irritability, tenderness on handling and sore mouth. The disease progresses slowly, and there are apparent quiescent intervals of varying length. As the disease continues, dyspnea and cyanosis develop owing to the pulmonary fibrosis, the primary symptoms become more marked, pathologic fractures may occur, the teeth become loosened and anemia develops as a result of the marked bone marrow displacement. Examination of the patient reveals punched-out areas of bone destruction and tenderness over the skull and the long bones. The spleen and liver are palpable but not markedly enlarged.

The blood is normal or shows mild secondary anemia early in the disease. With considerable involvement of the bone marrow an aplastic type of anemia may develop. There is no typical blood picture, and the xanthoma cell has not been found in the circulating blood.

Rowland stated that the cholesterol, lecithin and fatty acids of the blood are increased during the active stage but during the periods of apparent quiescence are normal. In other respects the blood chemistry has been found to be normal.

Routine laboratory tests give negative results. Roentgen examination shows multiple punched-out areas of bone displacement involving the membranous bones and often the long bones as well.

REPORT OF A CASE

Dorothy G., a 21 month old girl, was admitted to the University of Michigan Hospital in March, 1932, with a chief complaint of "anemia." Her birth was instrumental but uneventful; her development was normal, and the past history was entirely unimportant. The patient's mother was 21 years old, of French descent and healthy; the father was 24 years old, likewise of French descent and healthy. There was no family history referable to the xanthomatoses.

The present illness began at the age of 15 months, six months prior to admission, with the spontaneous appearance of a tumescence on the inferior border of the right mandible. This swelling appeared benign. There was no associated redness or heat, although there was some tenderness to palpation. The child had no coincident infection of the mouth or the upper respiratory tract, and the process

was unattended by fever. At this time the child fell and suffered a trauma to the left parietal region. A firm tumor which showed no tendency to involute developed at the site of the trauma. The child failed to gain weight and was restless and irritable. Three months after the onset of the illness the mandibular swelling disappeared, and coincident with its disappearance there was a small amount of foul-smelling, yellowish discharge from the right ear. Some swelling developed over the right mastoid area, and in the fourth month of the illness mastoidectomy

Fig. 1.—The patient on admission to the hospital.

was performed on the right side. The otologist found no pus at the time of operation but observed a small amount of yellowish granulation tissue. Shortly after the operation a pathologic fracture of the right femur developed, and the mother discovered a soft spot in the skull in the left parietal region at the site of the posttraumatic tumor. During the two months previous to admission progressive and marked anemia developed which necessitated repeated transfusions.

On admission the infant exhibited marked pallor. There was slight dyspnea. The pulse was rapid and thready. Over the scalp and in the midline of the chest

and of the back was a papulosquamous eruption covered with yellow, oily scales, confluent on the scalp and fairly discrete on the trunk. There was no excoriation indicative of pruritus over the involved skin. There was moderate edema of the ankles. Examination of the skull showed a mastoidectomy wound on the right with little evidence of healing. In the right parietal region there was a soft, punched-out area of bone destruction about 1 inch (2.5 cm.) in diameter. The lower right molars were loose, and the gums were spongy and injected. The tonsils were hypertrophic and septic. The lungs were normal. The heart was slightly enlarged; the rate was rapid; the sounds were of poor quality, and there was a soft blowing systolic murmur at the apex. The spleen was felt 1 inch below the left costal margin, and the edge of the liver was felt about 2 inches (5 cm.) below the right costal margin. There was genu valgum of the right leg, and pain and tenderness were noted on manipulation of the extremities. There was no remarkable lymphadenopathy. The urine was normal. The hemoglobin was 15 per cent (Sahli), and the erythrocyte count, 900,000. The leukocyte count was 7,000, and the smear showed 47 per cent neutrophils, 49 per cent lymphocytes and 4 per cent monocytes. The platelets were definitely decreased. The red

Fig. 2.—The patient a few days before death.

cells showed moderate achromia. Occasional stippled cells and nucleated red cells were found.

There was no gross lipemia. The blood cholesterol was 182 mg. per hundred cubic centimeters; phosphorus, 2.8 mg. and calcium, 9.4 mg. The serum protein was 5.2 Gm. per hundred cubic centimeters.

The tuberculin and the Kahn test of the blood were negative.

Roentgen examination of the skeletal system demonstrated multiple lesions of the skull, the right mandible, both scapulae, the left humerus and both lower extremities. These lesions were well defined areas of apparent complete decalcification.

Bone marrow smears were obtained by biopsy, and xanthoma cells were found.

The course of the disease while under my observation was essentially that of aplastic anemia. The anemia progressed, blood platelets became practically absent and the white blood cell count dropped to as low as 2,600, with 20 per cent neutrophils. There were marked purpura, frequent epistaxis and bleeding from the gums. Several transfusions were given with but transitory relief. The patient became more dyspneic than even the progressive anemia warranted, and during her last week in the hospital the oxygen tent was necessary. Owing to exsanguination, generalized anasarca gradually developed, and the child died on the fortieth day in the hospital.

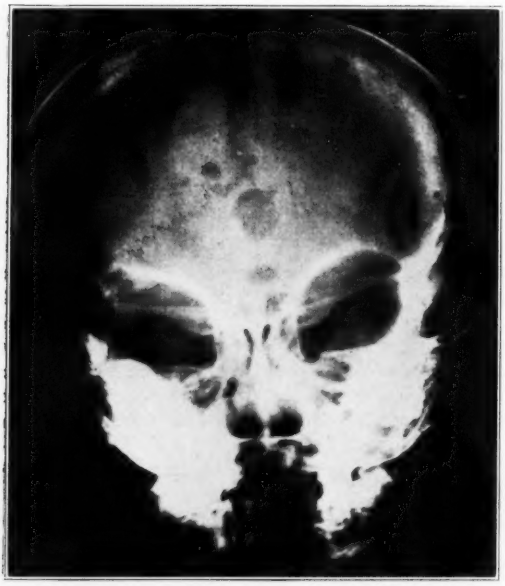

Fig. 3.—Anteroposterior roentgenogram of the skull showing multiple lesions of the calvarium and involvement of both mandibles, particularly the right.

Fig. 4.—Lateral view of the skull. The large temporal lesion was found on physical examination.

The results of pathologic examination, conducted by Dr. C. V. Weller, were as follows: The skull cap showed a soft, discolored area about an inch in diameter in the left parietal region. Several small yellow areas were observed in the inner table. There was a patchy thickening of the dura with small yellowish deposits on its inner surface. These areas of thickening were microscopically made up of young fibroblasts, reticulo-endothelial cells, small multinucleate giant cells and foam cells. There were similar deposits with dense adhesions along the periosteal surface. The hypophysis was essentially normal, but the sella turcica

Fig. 5.—Defects in both femurs with pathologic fracture and consequent genu valgum.

was almost entirely replaced by the yellowish xanthomatous material. The wings of the sphenoid and the temporosphenoid area were likewise markedly infiltrated by the same substance. There was no xanthomatous involvement of either orbit.

In the costovertebral gutter on the right was a yellow tumor the size of a half dollar involving the ninth rib. There was a similar area the size of a dime on the seventh rib on the left side. Examination of the heart disclosed a small yellowish mass on the anterior surface of the right auricle and a few minute yellowish areas at the base of the aortic valve, and on microscopic examination granulation tissue containing typical foam cells was found in the auriculoventricular sulcus.

The lungs were doughy. At the base of the left lung a small xanthoma was found. Microscopic examination of the lungs showed diffuse fibrosis, obliterating to various degrees most of the smaller bronchi (fig. 9). Some of the pulmonary

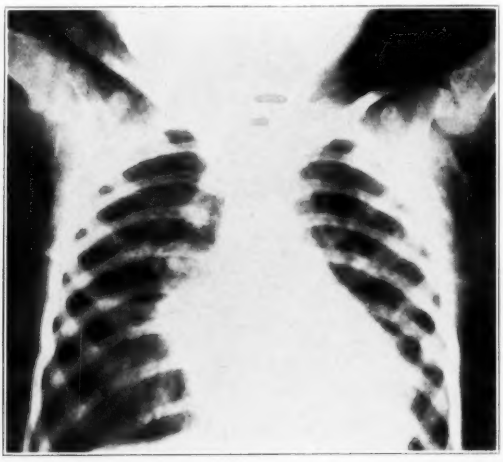

Fig. 6.—Anteroposterior view of the chest, showing lesions of both scapulae and marked increase of the hilar shadows due to xanthomatous infiltration and fibrosis.

Fig. 7.—Postmortem roentgenogram of the calvarium.

arteries showed calcification, and fat stains demonstrated lipoid-containing cells free in the alveolar spaces and present in small numbers about the vessels and bronchi (figs. 10 and 11).

The spleen was enlarged and microscopically showed marked congestion and localized areas of fibrosis containing foam cells and phagocytes loaded with brownish pigment. The liver was slightly smaller than normal, and fat stains showed no evidence of lipoidosis. Xanthomatous lesions were also found in the suprarenal cortex, the renal pelves and the long bones. In addition to the xanthomatous lesions there were marked calcification of the arteries, atrophy and parenchymatous degeneration of all organs, bilateral hydrothorax and ascites.

The clinical picture in this case of xanthomatosis differed from the usual one in several respects. Although there was considerable xantho-

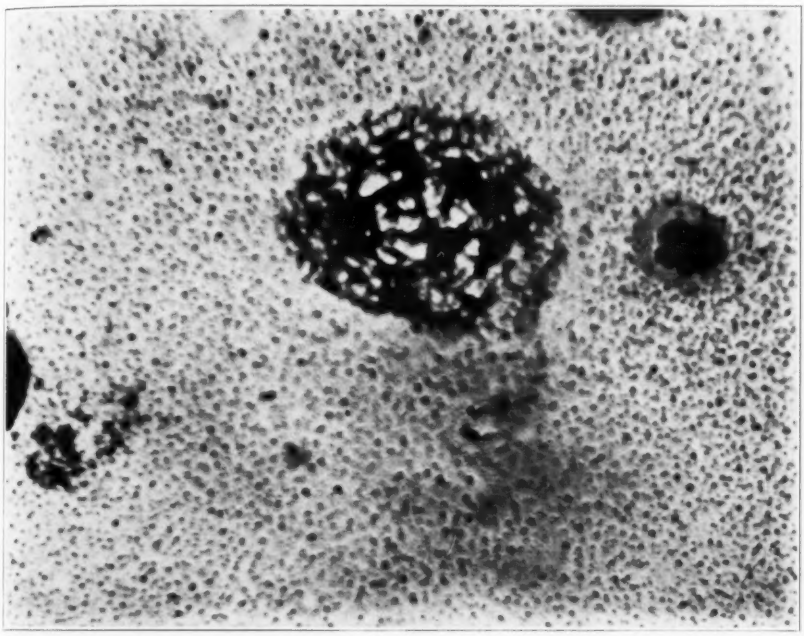

Fig. 8.—Foam cell (bone marrow).

matous infiltration at the base of the skull, particularly in the sella turcica, the pathologic changes in that region were apparently not great enough, or not of the proper form, to cause a reaction in the hypothalamic region sufficient to lead to the production of diabetes insipidus. However, had the patient lived longer, it is not unlikely that polyuria and polydipsia would eventually have developed. There was no pathologic evidence of xanthomatous involvement of the bony orbit, which adequately explains the absence of exophthalmos. The osseous lesions, both roentgenologically and pathologically, were characteristic of Schüller-Christian's disease. Although pathologic fracture is common

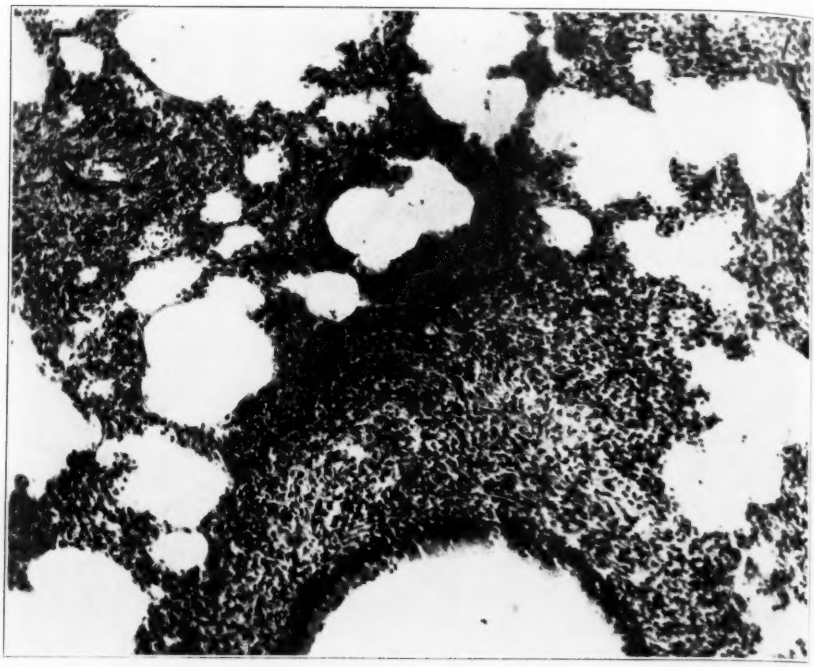

Fig. 9.—Pulmonary xanthomatosis and fibrosis.

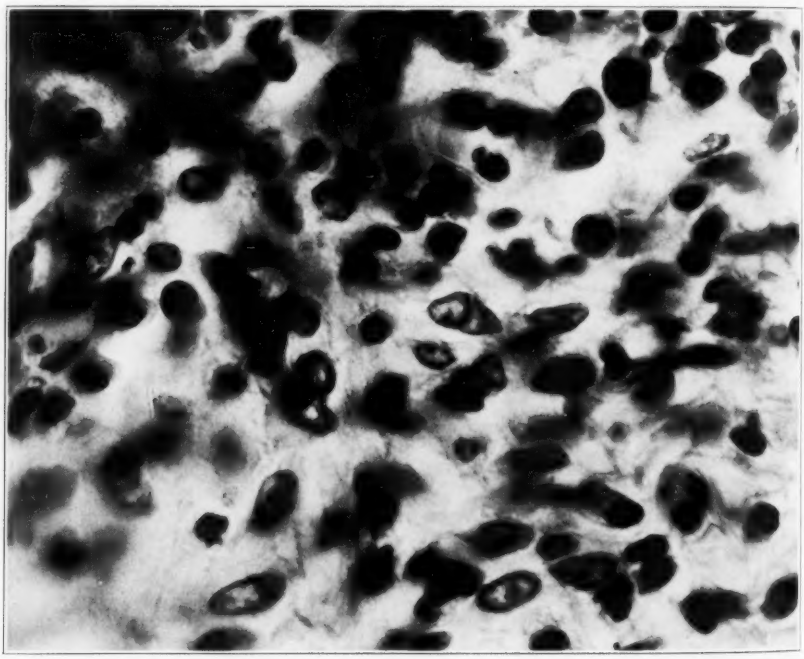

Fig. 10.—High power view of figure 9, showing foam cells and fibroblasts.

in Gaucher's disease, this case presents the first recorded instance of spontaneous fracture in the Schüller-Christian type of xanthomatosis.

The fact that xanthomatous infiltration of the temporal bone may simulate mastoiditis is well demonstrated in this case. A discharging ear developed, with postauricular tenderness and swelling. It is probable that had preoperative roentgen examination been made there would have been adequate roentgenologic evidence to rule out acute suppurative mastoiditis. That the operation was harmful in this case cannot be

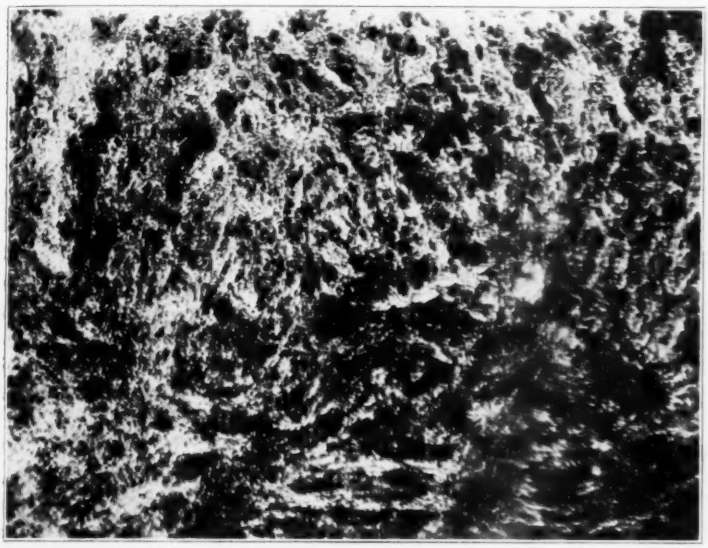

Fig. 11.—Osmic acid stain of a section of the lung, demonstrating the presence of considerable lipoid substance.

said with certainty, but it happened at a critical point in the illness, and the course after operation was rapidly downhill.

The severe aplastic anemia is commonly a part of the terminal stage of the disease, and reasonably so in view of the marked xanthomatous infiltration of the bone marrow. The marked hemorrhagic tendency was likewise a manifestation of inactivity of the marrow. Hemorrhagic phenomena are, however, more common in the terminal stages of the Gaucher's type of xanthomatosis than in Schüller-Christian's disease.

Cutaneous lesions have been described in a number of cases of the Schüller-Christian type of xanthomatosis. Rowland mentioned the pigmentation that may occur as a result of accumulation of lipochrome

pigments and stated that when present the eruption is primarily composed of pink papules which grow in size and become xanthomas. Microscopically these cutaneous lesions contain lipoid-laden foam cells. The eruption in this case was a typical seborrheic dermatitis, and no evidence of xanthomatous infiltration of the skin was found on microscopic examination.

There was no gross lipemia or cholesteremia in this case suggestive of faulty fat metabolism. Chemical examination of the blood showed a low normal calcium and a low phosphorus content although there was no evidence of rickets and the infant had received a balanced diet with adequate vitamin D previous to her illness. The marked arteriosclerosis was likewise interesting; it may be explained perhaps by the arterial deposition of calcium displaced by xanthomas from the bones by a mechanism similar to that occurring with huge doses of vitamin D.

The influence of diet on Schüller-Christian's disease is problematic. Rowland observed beneficial effects in one case in which the patient was on a low fat diet. His result is difficult to evaluate since patients with this disease at times have spontaneous remissions and Rowland administered pituitary and thyroid with the low fat diet. Wile, Eckstein and Curtis found in studying xanthomatosis of the skin that while a low fat diet has a beneficial effect in diabetic cases in which the lesions seem directly related to the lipemia there is no demonstrable relationship between blood fat and the lesions of essential xanthomatosis, and the amount of fat in the diet has no bearing on the course of the disease. Since there is close similarity between the Schüller-Christian and the essential type of xanthomatosis, particularly in that the clinical progress does not depend on the presence or degree of lipemia, in either type it seems logical that a low fat diet is probably of little therapeutic value.

Roentgen irradiation has been tried in a number of cases. Sossman reported good results, particularly in the tendency to involution of the osseous lesions under therapy. The difficulty, particularly in the case reported here, in which there was profound aplastic anemia, was in irradiating the lesions without producing further depression of the bone marrow.

LIPOIDS AND LIPOID DISEASES

III. LIPOID CONTENT OF TISSUES IN SCHÜLLER-CHRISTIAN'S DISEASE (XANTHOMATOSIS) AND REVIEW OF LITERATURE ON LIPOID CONTENT OF HUMAN TISSUES

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AND
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We present here a study of the lipoid content of the various tissues of the body in a case of Schüller-Christian's disease together with a review and discussion of the literature to date. Because of the severe anemia encountered in this case we include a parallel study on the tissue of a child of about the same age with similar anemia due to another cause. It was our idea that the latter might in a way act as a control. It has been our hope that should a case of accident come to autopsy we could present our own normal figures. This opportunity has not presented itself.

METHODS

The material was obtained from the autopsy table as soon as possible. All extraneous blood and tissue were carefully removed. None of the tissue was perfused. It was ground in a meat grinder and weighed. It was then placed in 95 per cent alcohol, the volume being at least three times that of the tissue. The air in the flasks was replaced by nitrogen. The tissue was allowed to remain in the alcohol for forty-eight hours. The alcohol was then decanted, fresh 95 per cent alcohol added and the mixture allowed to stand for forty-eight hours. Again the supernatant alcohol was decanted and absolute alcohol added. This was allowed to stand for three days, after which the alcohol was replaced by fresh absolute alcohol. The extraction with absolute alcohol was repeated, and the combined decantations were filtered. The tissue residue was rinsed with ether at least three times. It was then dried in a vacuum desiccator, after which it was ground finely in a coffee grinder. The ground residue was refluxed with absolute alcohol, two portions of alcohol being used. The material was refluxed for from thirty-six to seventy-two hours, depending on the amount of tissue examined. The tissue residue was again thoroughly rinsed with ether.

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Chloroform was used after the extraction in the first few analyses. The amount of lipoid extracted by this means was negligible. This step in the procedure was subsequently discontinued. The combined alcohol and ether extracts from the hot and cold methods were concentrated in

TABLE 1.—*Lipoids in Various Tissues in Case 1*

Tissue	Pathologic Changes	Weight of Sample, Gm.	Total Lipoid, Gm. per 100 Gm. Fresh Tissue	Phospholipoid, Gm. per 100 Gm. Fresh Tissue	Cholesterol, Gm. per 100 Gm. Fresh Tissue	Phospholipoid-Cholesterol Ratio
Liver	No lipoidosis; atrophy; increased stroma	150	3.17	2.24	0.398	6:1
Left lung	Diffuse fibrosis, mainly perivascular and peribronchial; phagocytes containing lipoid in these areas and in alveoli	65	3.01	1.69	0.432	3.9:1
Spleen	Congestion; localized areas of fibrosis containing foam cells and phagocytes loaded with brown pigment	35	2.36	1.53	0.286	5.3:1
Kidneys (one half of each)	Cloudy swelling; calcification of renal vessels and calcium deposits in tubules (no lipoidosis)	40	2.40	1.33	0.250	5.3:1
Suprarenal gland (entire gland)	Atrophy; medulla proportionally abundant	1.4	7.07	1.25	2.08	1:1.7
Heart (ventricular wall)	Serous atrophy of subpericardial fat; subendocardial degenerative fatty infiltration	11	2.66	1.82	0.174	10.5:1
Psoas muscle	Very edematous; pale	13	0.90	0.47	0.128	3.7:1
Rectus muscle	Very edematous; pale	8	0.84	0.47	0.110	4.3:1
Bone marrow (distal end of femur, approximately normal)	Cellular, hyperplastic marrow in some areas; edematous fibrous connective tissue in others	7.3	3.01	1.04	0.664	1.6:1
Xanthoma from proximal end of femur	Yellow, tough and fibrous; no resemblance to normal bone marrow; similar to xanthoma in dura	4.4	7.39	1.59	4.023	1:2.6
Xanthomata (small masses from orbital, occipital and temporal regions; approximately 10% of weight is adherent dura and periosteum)	Localized areas of thickening containing young fibroblasts, reticulo-endothelial cells, small multinucleated giant cells and many foam cells	1	6.96	0.83	3.462	1:4.2

vacuo to a convenient volume. Adequate samples were then evaporated almost to dryness and redissolved in purified petroleum benzine (20°—40° redistilled). The solution was washed with water to remove any water-soluble material, such as pigments. It was then made up to a convenient volume, and samples were used for the determination of total lipoid, cholesterol and phospholipoid.

For the determination of total lipoid, an aliquot part of the solution was placed in a weighed dish, the ether evaporated and the weight of the residue determined. For the determination of lipoid phosphorus, the Whitehorn [1] method was used. The phospholipoid content was estimated by multiplying the amount of lipoid phosphorus by the factor 26. For the determination of cholesterol, Sackett's [2] method was used. Duplicate tests were made in all determinations.

REPORT OF CASES

CASE 1.—*D. G., aged 21 months. Schüller-Christian's disease.*

A complete clinical and pathologic report of this case was given in the preceding paper in this series by Lichty [3] and will not be repeated here. The pathologic diagnosis was: Schüller-Christian's disease; localized cholesterol ester lipoidoses in the dura, skull cap, base of the skull, pituitary fossa, ribs, right femur, thymic area, lungs, subpericardial tissues, submucosa of the renal pelves and skin and in many lymph nodes; bony defects in the skull cap, seventh and ninth ribs, mandible and right femur; patchy fibrosis of the lungs; marked calcification of the arteries; anemia; petechial hemorrhages in the skin, right lung and pericardium; atrophy and parenchymatous degeneration of all organs; bilateral hydrothorax; ascites. The results of the determinations of lipoids are recorded in table 1.

CASE 2.—S. B., aged *10 months. Severe secondary anemia with delayed maturation of the red blood cells.*

The child was admitted to the clinic because of progressive loss of weight for two or three months and anorexia, regurgitation and diarrhea for two weeks before entrance.

On examination she was very irritable. The skin showed a peculiar yellowish color, but there was no definite icterus. There was evidence of loss of weight, but the panniculus was still thick, particularly over the lower extremities. The tone of the skin was gone, and the skin hung in folds filled with firm fat. The gums were tender, with some bleeding along the alveolar ridge. The glands, lungs, heart and abdomen were essentially normal. There was bilateral knee jerk clonus. The other reflexes were normal. Ophthalmoscopic examination showed that the disks in both eyes were slightly edematous and had a grayish-ashen hue. Roentgen examination of the long bones showed nothing abnormal. The urine was normal. The blood chemistry is recorded in tables 2 and 3. The patient was given one transfusion of 90 cc. of blood, which was followed by a rise in temperature. Soon after this signs of bronchopneumonia developed, and the child died on the tenth day in the hospital.

The pathologic diagnosis was: Anemia of undetermined origin resembling pernicious anemia; terminal bronchopneumonia; asphyxiative death; aspiration of food into the respiratory passages; petechial hemorrhages into the lungs and meninges; acute passive congestion of all organs; fatty infiltration of the liver; terminal cardiac dilatation; fibroid atrophy of the thymus. The results of the analysis of tissues are recorded in table 4.

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1. Whitehorn, J. C.: J. Biol. Chem. **62**:133, 1924.
2. Sackett, G. E.: J. Biol. Chem. **64**:203, 1925.
3. Lichty, D. E.: Lipoids and Lipoid Diseases: I. Xanthomatosis (Schüller-Christian Type), Arch. Int. Med., this issue, p. 379.

TABLE 2.—*Findings in Blood*

	Schüller-Christian's Disease	Severe Secondary Anemia
Hemoglobin	45%	47-44%
Red cells	1,500,000	3,710,000-1,780,000
Color index	1.5	1.46
White cells	3,500	11,100-9,600
Reticulocytes	++	++
Polymorphonuclears	50%	64.2-48%
Large lymphocytes	20%	12.5%
Small lymphocytes	30%	10%
Total lymphocytes	50%	54-28.5%
Monocytes	9%	1%
Eosinophils	0%	1%
Anisocytosis	+	+
Poikilocytosis	+	++
Stippled red cells	+	+
Nucleated red cells	+	+
Pencil forms	—	+
Myelocytes	±	0
Macrocytes	++	++
Microcytes	+	—
Achromia	0	+
Polychromatophilia	+	—
Platelets	±	+ normal

TABLE 3.—*Blood Chemistry*

	Schüller-Christian's Disease	Severe Secondary Anemia	Comment
Nonprotein nitrogen	23	40	Case of Schüller-Christian's disease showed calcification of renal vessels, calcified thrombus, lime salt deposit in some tubules and calcification of suprarenal arteries; no such changes in case of anemia
Sodium chloride	533	505	
Cholesterol	182-160	110	
Phospholipoid	...	112	
Total lipoid	...	429	
Serum calcium	9.4	9.7	
Serum phosphorus	2.8	3.8	
Carbon dioxide-combining power	39% by volume		
Serum protein	5.2 Gm.		
Serum albumin	2.7 Gm.		
Serum globulin	2.5 Gm.		
Blood group	II	IV	
Kahn test	0	0	

TABLE 4.—*Lipoids in Various Tissues in Case 2*

Tissue	Pathologic Changes	Weight of Sample, Gm.	Total Lipoid, Gm. per 100 Gm. Fresh Tissue	Phospholipoid, Gm. per 100 Gm. Fresh Tissue	Cholesterol, Gm. per 100 Gm. Fresh Tissue	Phospholipoid-Cholesterol Ratio
Liver	Cloudy swelling; fatty infiltration	56.5	8.09	1.79	0.280	6.4:1
Lungs	In lower lobes, aspiration pneumonia and abundant fat droplets in bronchi and alveoli; upper lobes grossly showed very slight involvement; upper lobes used for analysis	17	4.62	1.33	0.335	4:1
Spleen	Congestion	8	3.64	1.43	0.337	4.3:1
Kidneys (one half of each)	Passive congestion; cloudy swelling	18.5	4.02	1.14	0.362	3.2:1
Heart (ventricular wall)	Hypoplasia of muscle	5.5	4.19	1.43	0.118	12.1:1
Rectus muscle	Congestion	9	5.9	0.49	0.121	4:1

COMMENT

The lipoids in the tissues in our case of Schüller-Christian's disease (table 1) showed no marked differences from those of normal persons, except in the xanthomatous masses. The results of analysis of these masses are in agreement with the figures recorded by Epstein and Lorenz [4] and by Kleinman.[5] The lipoid content was high (from 6.96 to 10.37 Gm. per hundred grams of tissue). At least from 40 to 50 per cent of the total lipoid was cholesterol. The cholesterol content of the xanthomata was much higher than that found in the various normal tissues. The phospholipoid content (from 0.45 to 0.83 Gm.) was much lower than that found in the other tissues of the body examined and than that found in normal tissue with the exception of voluntary muscle.

The proximal end of the right femur was the site of a xanthoma one-third the length of the femur (shown in the roentgenogram [fig. 5] in the preceding article [3]) which had practically replaced the marrow. At the distal end of the bone the marrow appeared more nearly normal. The total lipoid content of the xanthoma (7.386 Gm. per hundred grams of tissue) was found to be twice that of the marrow at the distal end of the bone (3.013 Gm.). The cholesterol content of the xanthoma (4.023 Gm.) was six times as great. On the other hand, the phospholipoid content of the xanthoma (1.59 Gm.) was distinctly higher than that of the marrow of the distal end of the bone (1.047 Gm.). The total lipoid and the cholesterol content of the xanthoma of the bone marrow were very similar to those of the dura. The phospholipoid of the xanthoma of the bone marrow was almost twice as great as that of the xanthoma from the dura. No explanation for this difference is at hand.

In table 5 will be found a review of the literature on the total lipoid, phospholipoid and cholesterol content of human tissues. The analyses are so arranged as to be easily compared with the results that we have obtained in the two cases presented. We were unable to use the figures in several reports because the determination of the lipoid content was on the basis of grams per hundred grams of dried tissue, and the percentage loss of water was not given. In some of the reports the water content was given. This enabled us to calculate the lipoid content in terms of grams per hundred grams of wet tissue, this being the basis of our analysis.

By reference to table 5 it will be seen that Kleinman reported a high cholesterol content in the liver and spleen in his case of Schüller-Christian's disease, while we were unable to show an increase above

4. Epstein, E., and Lorenz: Ztschr. f. physiol. Chem. **192**:145, 1930.
5. Kleinman, H.: Virchows Arch. f. path. Anat. **282**:613, 1931.

TABLE 5.—*Lipoid Content of Human Tissues as Reported in the Literature*

Tissue	Age	Reporter	Pathologic Diagnosis	Total Lipoid, Gm. per 100 Gm. Fresh Tissue	Phospholipoid, Gm. per 100 Gm. Fresh Tissue	Cholesterol, Gm. per 100 Gm. Fresh Tissue	Phospholipoid-Cholesterol Ratio
Liver	8 mos. fetus	Beumer [7]	.....	3.34	....	0.285	
	5½ yrs.	Beumer	Pulmonary and meningeal tuberculosis	4.44	....	0.341	
	11 mos.	Beumer	von Jaksch's anemia	2.85	....	0.180	
	22 yrs.	Theis: J. Biol. Chem. **82**: 327, 1929	Normal	3.04	1.79		
	35 yrs.	Theis	Normal	3.45	1.71		
	Died at birth	Theis	.....	5.16	1.71		
	20 yrs.	Fex: Biochem. Ztschr. **104**: 82, 1920	Normal	....	....	0.324	
	29 yrs.	Fex	Normal	....	....	0.377	
	30 yrs.	Fex	Normal	....	....	0.254	
	10 mos.	Authors' case	Secondary anemia (fatty degeneration of liver)	8.09	1.79	0.280	6.4:1
	2 yrs.	Authors' case	Schüller-Christian's disease	3.17	2.24	0.398	6:1
	3 yrs.	Kleinman [5]	Schüller-Christian's disease	4.46	0.291	1.060	1:3.6
Spleen	3 mos. fetus	Beumer [7]	.....	1.95	....	0.368	
	8 mos. fetus	Beumer	.....	1.83	....	0.306	
	6 yrs.	Beumer	Polyarthritis; secondary anemia	3.284	....	0.235	
	Infant	Kleinman [5]	Normal	1.108	0.297	0.162	1.8:1
	10 mos.	Authors' case	Secondary anemia	3.64	1.43	0.337	4.3:1
	3 yrs.	Kleinman [5]	Schüller-Christian's disease	1.07	0.254	0.794	1:3.1
	2 yrs.	Authors' case	Schüller-Christian's disease	2.36	1.53	0.286	5.3:1
Lungs	3 mos. fetus	Beumer [7]	.....	1.47	....	0.188	
	8 mos. fetus	Beumer	.....	1.30	....	0.166	
	10 mos.	Authors' case	Anemia; terminal bronchopneumonia	4.62	1.33	0.335	4:1
	2 yrs.	Authors' case	Schüller-Christian's disease	3.01	1.69	0.432	3.9:1
Kidneys	.....	Windaus: Ztschr. f. physiol. Chem. **65**: 110, 1910	Normal	2.06	....	0.272	
		Windaus	Normal	1.87	....	0.250	
	8 mos. fetus	Beumer	.....	2.87	....	0.275	
	6 yrs.	Beumer	Polyarthritis; secondary anemia	4.25	....	0.134	
	11 mos.	Beumer	von Jaksch's anemia	3.17	....	0.199	
	20 yrs.	Fex: Biochem. Ztschr. **104**: 82, 1920	Normal	....	....	0.310	
	29 yrs.	Fex	Normal	....	....	0.340	
	30 yrs.	Fex	Normal	....	....	0.293	
	10 mos.	Authors' case	Secondary anemia	4.02	1.14	0.362	3.2:1
	2 yrs.	Authors' case	Schüller-Christian's disease	2.40	1.33	0.250	5.3:1

	10 mos.	Authors' case	Secondary anemia	4.02	1.14	0.362	3.2:1
	2 yrs.	Authors' case	Schüller-Christian's disease	2.40	1.33	0.250	5.3:1

Suprarenals	8 mos. fetus	Beumer		2.90	....	0.358	
	6 yrs.	Beumer	Polyarthritis; secondary anemia	14.626	....	1.099	
	20 yrs.	Fex: Biochem. Ztschr. **104**: 82, 1920	Normal	....	....	6.664	
	29 yrs.	Fex	Normal	....	....	2.595	
	30 yrs.	Fex	Normal	....	....	5.003	
	2 yrs.	Authors' case	Schüller-Christian's disease	7.07	1.25	2.08	1:1.7
Pectoral muscle	.....	Jewett: Biochem. J. **25**: 1991, 1931	Normal	8.74	0.667	0.351	1.9:1
		Jewett	Normal	7.28	0.53	0.377	1.4:1
Rectus abdominis muscle	10 mos.	Authors' case	Secondary anemia	5.90	0.49	0.121	4:1
	2 yrs.	Authors' case	Schüller-Christian's disease	0.90	0.47	0.128	3.7:1
Psoas muscle	2 yrs.	Authors' case	Schüller-Christian's disease	0.84	0.47	0.110	4.3:1
Heart muscle	3 mos. fetus	Beumer		3.91	....	0.193	
	8 mos. fetus	Beumer		3.10	....	0.173	
	10 mos.	Authors' case	Secondary anemia	4.19	1.43	0.118	12.1:1
	2 yrs.	Authors' case	Schüller-Christian's disease	2.66	1.82	0.174	10.5:1
Bone marrow	16 mos.	Gliken: Biochem. Ztschr. **4**: 235, 1907	Bronchopneumonia	8.00	1.99		
	7 mos.	Gliken	Pneumonia	2.48	1.52		
	61 yrs.	Gliken	Influenza	68.4	1.38		
	8 mos. fetus	*Beumer		12.264	....	0.056	
	2 yrs.	Authors' case	Schüller-Christian's disease	3.013	1.04	0.664	1.6:1
Xanthomas	.....	Epstein and Lorenz [4]	From dura mater	9.554	0.45	5.119	1:11.4
	3 yrs.	*Kleinman [5]	From dura mater	10.39	0.72	4.23	1:6
	2 yrs.	Authors' case	From dura mater	6.96	0.83	3.462	1:4.2
	2 yrs.	Authors' case	Of bone marrow	7.386	1.59	4.023	1:2.6

* Calculated from analysis of dry tissue and recorded percentage of loss of water.

normal. This is probably due to a greater lipoid involvement of these organs in his case (Jghanti[6]). Tissue similar to that found in the xanthoma of the skull was found in the liver and spleen. There were only a few areas of normal spleen left, while in our case the splenic involvement consisted of only a few localized areas of fibrous tissue containing foam cells. There was no lipoidosis in the liver and spleen in our case.

In Kleinman's case the phospholipoid content of the liver and spleen was much lower than that found in our case.

Kleinman spoke of a reversal of the phospholipoid-cholesterol ratio in Schüller-Christian's disease. We have been unable to determine the normal ratio of these substances in the tissues, and there are not sufficient data in the literature to establish it. The ratios that we obtained in our case of Schüller-Christian's disease and in our case of anemia were from 3.2 : 1 to 6.4 : 1, except for the heart, which showed a higher ratio (10.5 : 1 and 12 : 1).

When we compare the lipoid content of the various tissues in Schüller-Christian's disease with the values for normal tissue that we have found in the literature, we are impressed with the similarity in the kidneys, liver, spleen and heart muscle. On the other hand, in the lungs the cholesterol was higher; in the skeletal muscle the total lipoid and cholesterol were very low, and in the suprarenals the total lipoid and cholesterol were higher. It should be remembered that the normal tissue used for comparison of values in the heart muscle, suprarenals and lungs came from the fetus, and accordingly satisfactory comparisons cannot be made. We do not know the effect of the aging process on the lipoid content of the various tissues. We observe that in one case, recorded by Beumer[7] (table 5), the total lipoid content of the suprarenals of a 6 year old child was 14.6 Gm. per hundred grams of tissue, while that recorded by the same author for an 8 month fetus was only 2.9 Gm. The same wide variation is noted in the cholesterol content (1.099 Gm. as compared with 0.358 Gm. in the 8 month fetus).

Because of the severe anemia in our case of Schüller-Christian's disease we were interested to see what the comparative lipoid contents of the tissues in a case of equally severe anemia not associated with xanthomatous involvement might be. These comparisons will be better seen by reference to table 5, in which we have arranged the cases together under each caption. There is a similarity in the liver, spleen, kidneys and heart muscle. In the lungs of the patients with Schüller-Christian's disease the cholesterol was higher; in the striated muscle the

6. Jghanti, W. K.: Virchows Arch. f. path. Anat. **282**:585, 1931.
7. Beumer, H.: Monatschr. f. Kinderh. **19**:409, 1921.

total lipoid was lower.[8] In these comparisons the factor of age does not enter. The comparison of the anemias may be seen in table 2; at the time of death in each case the color index was above 1 and the differential counts were similar in many ways. The blood chemistry also showed many points of similarity (table 3).

CONCLUSIONS

1. The analysis of the total lipoid, cholesterol and phospholipoid content of the various tissues in a case of Schüller-Christian's disease and in one of severe anemia, for comparison, are recorded. We have also given a review of the literature on the lipoid content of human tissue that could be brought into close comparison with the methods that we employed.

2. No significant changes were found in the lipoid content of the tissues in the case of Schüller-Christian's disease except where the xanthomatous masses were located.

3. The xanthomatous masses had a high content of total lipoid, 50 per cent of which was cholesterol. The xanthomata of the bone marrow contained an amount of total lipoid and cholesterol similar to that found in the xanthomatous processes in other locations. The widespread lesions were in the bone marrow. Our observations confirm those of Epstein and Lorenz and Kleinman on xanthomata of the dura.

4. These observations record the condition of the tissues at the end of a prolonged clinical process. We know of no observations on the lipoid content of the tissues in the earlier stages of the disease.

8. There was considerable edema in this tissue. The anemia in this case was of much longer duration.

ARTERITIS OF THE TEMPORAL VESSELS

A PREVIOUSLY UNDESCRIBED FORM

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Arteritis of the temporal vessels is unusual, and a new clinical syndrome, the etiology of which is still obscure, is probably represented in the two cases which form the basis of this report. These are the only cases which have been observed at the Mayo Clinic, and we have not noted reports of similar cases in the literature. A name cannot be given to this condition until more cases have been observed and the condition is dignified by nomenclature.

REPORT OF CASES

CASE 1.—An unmarried woman, aged 50, was first admitted to the clinic in May, 1917. General examination at that time gave negative results. The blood pressure in millimeters of mercury was 129 systolic and 78 diastolic. At the second admission, in September, 1927, the physical examination and laboratory tests disclosed an enlarged uterus, sclerosis, graded 1, of the retinal arteries and a blood pressure of 216 systolic and 126 diastolic. At the third admission, in December, 1927, the blood pressure was 200 systolic and 125 diastolic. The patient came the fourth time, on March 1, 1928, because she had colic of the left kidney. Cystoscopic examination revealed a stone in the left ureter, which was removed by manipulation. The blood pressure was 170 systolic and 98 diastolic. A diagnosis of fibroid uterus had been made previously, and because of excessive and irregular menses, total abdominal hysterectomy, bilateral salpingectomy, bilateral ovariectomy and appendectomy were performed. Recovery was uneventful. At the fifth admission, on June 14, 1928, the blood pressure was 230 systolic and 120 diastolic. Sclerosis, graded 1, of the retinal arteries was present. The results of laboratory tests made as a routine were negative. The patient's chief complaint at her sixth admission, on Nov. 20, 1928, was of headaches in the morning for two and a half months. Hourly observations of the blood pressure revealed a range of from 195 to 250 systolic and of from 100 to 130 diastolic. The concentration of hemoglobin was 72 per cent (Dare); erythrocytes numbered 4,890,000 and leukocytes, 5,900 in each cubic millimeter of blood. The value for urea was 25 mg. and for creatinine, 1.7 mg. in each hundred cubic centimeters of whole blood (method of Folin). The return of phenolsulphonphthalein in the urine was 50 per cent in two hours; albumin, graded 2, was present. Electrocardiograms gave evidence of left ven-

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tricular preponderance, a diphasic T-wave in derivation I and an inverted T-wave in derivations I, II and III.

Observations at the patient's seventh admission, on March 16, 1931, were of particular interest. She complained of soreness of the scalp, painful nodules along the temporal arteries, anorexia, loss of weight and headaches of six weeks' duration. She remained under observation for forty-two days. A few small, painful nodules were still present in the left temporal region, along the superficial temporal artery. They recurred from time to time during her stay in the hospital. The temperature by mouth ranged from 98 to 103 F.; the pulse rate was from 80 to 120 beats a minute. Leukocytes varied from 7,500 to 13,700, the concentration of hemoglobin was 40 per cent (Dare), and erythrocytes numbered 3,620,000. The differential leukocyte count was normal, and repeated examinations of the blood gave no additional significant findings. The general physical examination gave essentially negative results except for compensatory cardiac hypertrophy, graded 1, and retinal and peripheral sclerosis, graded 2. The patient was mentally alert, but during this period she had frequent severe headaches which differed from the morning headaches previously referred to. Otherwise she had no definite aches or pains. Hourly records of blood pressure, with the patient at rest, showed a range of from 140 to 190 systolic and of 65 to 100 diastolic. A roentgenogram of the head revealed that the sella turcica was enlarged, graded 3, and that the floor and posterior clinoid processes were eroded. Neurologic examination gave objectively negative results, as did that of the cerebrospinal fluid. The visual fields were normal. Urinalysis, made repeatedly, gave negative results except that it disclosed traces of albumin. The result of the serologic test for syphilis was negative. Cultures of the blood, made on March 27, April 9 and April 27, and cultures of the urine gave negative results. The results of inoculation of guinea-pigs with urine catheterized from the bladder were negative. In the stained sediment of the urine, bacilli of tuberculosis were not found. Agglutination for undulant fever, typhoid fever and paratyphoid fever A and B was negative. Examination of the sputum disclosed nothing abnormal. The basal metabolic rates were — 15 and — 12. A proctoscopic examination gave negative results. An electrocardiogram disclosed that the cardiac rate was 95 beats each minute, sinus tachycardia was present, and there were left ventricular preponderance, a notched P wave in derivation III and a slurred QRS complex in derivations I and III. Analysis of the gastric content in terms of cubic centimeters of tenth normal sodium hydroxide revealed a total acidity of 54 and free hydrochloric acid of 34. The return of phenolsulphonthalein in the urine was 70 per cent in two hours. The value for urea was 28 mg. in each hundred cubic centimeters of blood. Roentgenograms of the kidneys, ureters and bladder, right hip, thorax, stomach, small intestine and colon were negative. A segment from one of the thrombosed left temporal arteries was removed for biopsy, for cultures, and for special study, results of which will be reported later in this paper. The treatment instituted will also be discussed later.

The patient was under observation again in June, July and August, 1931. The temperature by mouth was from 99.5 to 100 F. in the afternoon, and the pulse rate was from 90 to 100 beats each minute. During this period painful nodules recurred along the temporal vessels with the usual systemic effects. The patient was hospitalized on September 23 and remained in the hospital for two days. The tenderness of the scalp and temporal regions entirely disappeared. The temperature became normal, and the blood picture improved; the concentration of hemoglobin was 11.1 Gm. in each hundred cubic centimeters of blood. Erythrocytes numbered 4,340,000 and leukocytes 6,000 in each cubic millimeter of blood. The differential

leukocyte count was normal. The blood pressure was 230 systolic and 125 diastolic. The patient remained in good health until the spring of 1932, when cardiac and renal insufficiency developed and she was hospitalized for forty days. Following this she remained well until November, 1932, when again tender areas along the left temporal artery developed.

The patient was again observed at the clinic on Dec. 3, 1932. The left superficial temporal artery was more prominent and tortuous than the right and small segments about 1 cm. in length were tender, but still pulsated. Definite nodules were not present. The walls of the vessel in the tender regions felt thicker than

Fig. 1 (case 1).—Cross-section of an occluded vessel. Marked thickening of the intima almost to the point of occluding the vessel can be observed. A granulomatous area with almost complete destruction of the media is present (*a*); × 55.

the adjacent proximal and distal segments. The temperature by mouth was 98.2 at 11 a. m., and the blood pressure was 200 systolic and 120 diastolic. Laboratory tests were not carried out.

The patient's final admission was on Feb. 27, 1933; she came because of congestive heart failure and marked renal insufficiency. The painful areas over the scalp and along the temporal vessels had not recurred since December, 1932. She was under observation for thirty-two days, but little clinical improvement was noted. The value for urea fell from 62 mg. on admission to 32 mg. in each hundred cubic centimeters of whole blood. Daily urinalysis revealed albumin graded from 3 to 4 and a few casts. No change was observed in the ocular fundi or sella

turcica from that which was observed on the previous examinations. The visual fields were normal. Roentgenograms of the thorax revealed that the heart was enlarged, graded 4. The electrocardiogram revealed sinus rhythm, left ventricular preponderance (marked), inverted T waves in derivation I, exaggerated P waves in derivations II and III and slurred QRS complexes in derivations I, II and III. The blood pressure ranged from 160 to 190 systolic and from 80 to 130 diastolic. The patient gradually failed after she returned to her home and died approximately a month later. Necropsy was not performed.

CASE 2.—A man, aged 68, of Irish parentage, registered at the clinic on May 25, 1931. He had always had excellent health until the onset of the illness for which he sought treatment. His chief complaints were weakness and painful and tender areas over the scalp, which had been present for four weeks. At the onset pain around the teeth and stiffness of the jaw had developed. A week later pain had developed in the forehead and frontal area, with marked tenderness and a feeling of warmth in these areas. These symptoms were present daily. He did not know if the temperature was elevated. He had lost 25 pounds (11 Kg.).

Physical examination revealed that the patient was undernourished, appeared to be anemic, and weighed 140 pounds (63 Kg.). Red, raised, tender areas were present along the superficial temporal arteries. The cervical lymph nodes were moderately enlarged. Dental examination revealed periapical infection, graded 3; nine teeth were involved and pyorrhea was marked. The blood pressure in millimeters of mercury was 165 systolic and 90 diastolic. The temperature by mouth ranged from 99.3 to 100 F. Urinalysis gave negative results. The concentration of hemoglobin was 12.1 Gm. in a hundred cubic centimeters of blood; erythrocytes numbered 3,730,000 and leukocytes 10,600 in each cubic millimeter of blood. The differential leukocyte count was normal. The serologic test for syphilis gave a negative result. Roentgenograms of the thorax revealed that the heart was enlarged, graded 1. Roentgenograms of the sinuses gave evidence of a slight thickening of the membrane of the right antrum. The electrocardiogram showed that the function was normal.

A large segment of a thrombosed artery was removed from the left temporal region for cultures and special study. The infected teeth were removed during the patient's stay in the clinic. Cultures from the apexes did not reveal growth of organisms or fungi.

A letter from the patient dated Oct. 30, 1932, stated that he had had his remaining teeth extracted shortly after he returned to his home, without any untoward effects, and that he had remained well since then. There had been no recurrence of the pain along the temporal vessels.

SPECIAL STUDIES

The bacteriologic studies of the resected temporal arteries were of particular interest, and presented some significant findings.

The specimen from case 1 did not yield growth of any of the organisms which one might expect to find as contaminants, but on the third day it yielded from thirty to fifty colonies per agar unit of a rather unusual growth on the solid mediums, many different kinds of mediums having been employed. The broth cultures were sterile, again indicating lack of contamination by the ordinary bacteria. On further study it became obvious that the organism which had grown on culture

was Actinomyces. Sections of the artery stained with Gram stain revealed minute filamentous, gram-positive material which could easily be interpreted as being mycelia. This appearance was emphasized by the granulomatous-like lesion. At this stage in the study the second

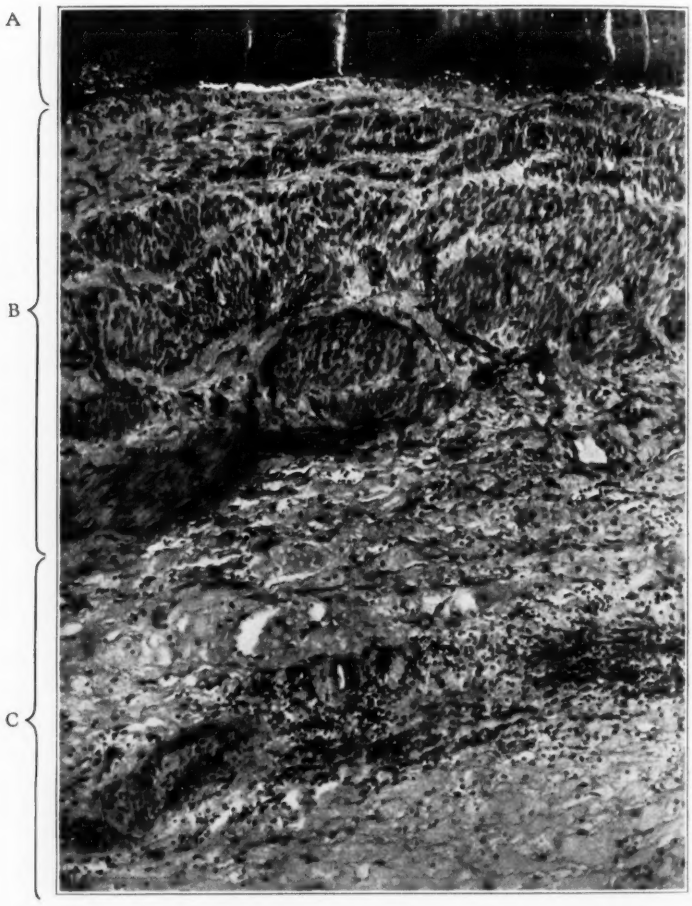

Fig. 2 (case 2).—Cross-section of occluded vessel. The lumen (*A*) is filled with an acute thrombus. Marked periarteritis with infiltration of the adventitia (*C*) with round cells is present. *B* is the media. × 120.

specimen was procured and, on similar treatment, identical results were obtained. We now had two specimens from similar cases of an unusual nature yielding identical organisms of a type not usually encountered.

They differed from all other described Actinomyces recovered from man; in the absence of any obvious evidence of contamination, it appeared that there might be some etiologic connection between the organism found and the lesion produced. However, the Actinomyces found seemed to be exactly like common Actinomyces found in the soil and not like that found in lesions of animals. We, therefore, began a search for possible sources of contamination. Although the sand which was used to grind the organism had been sterilized at 170 C.

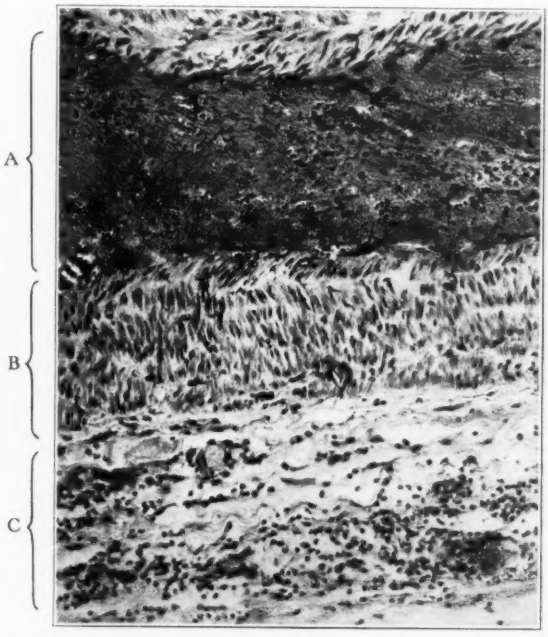

Fig. 3 (case 2).—Longitudinal section of a small occluded artery. The lumen (*A*) is filled with an acute thrombus. Marked infiltration of the adventitia (*C*) with round cells is present. *B* is the media. × 140.

(338 F.) for one hour, we obtained from similar batches of sand treated in the same way and from dust in the room the same type of Actinomyces as we had previously found in the cultures of the two specimens. Whether the organism was introduced with the sand, whether it came from the dust of the room during the course of handling the material, or whether it was originally in the tissue, we cannot say, but the evidence is that this organism is a soil Actinomyces, and that it can be obtained as a contaminant under these standard conditions of procedure.

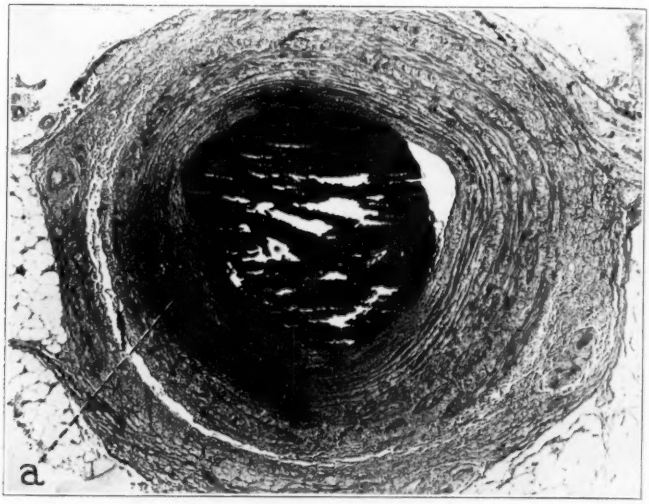

Fig. 4 (case 2).—Cross-section of an occluded vessel. The lumen is filled with an acute thrombus. Hemorrhage into the media (*a*) is seen. × 28.

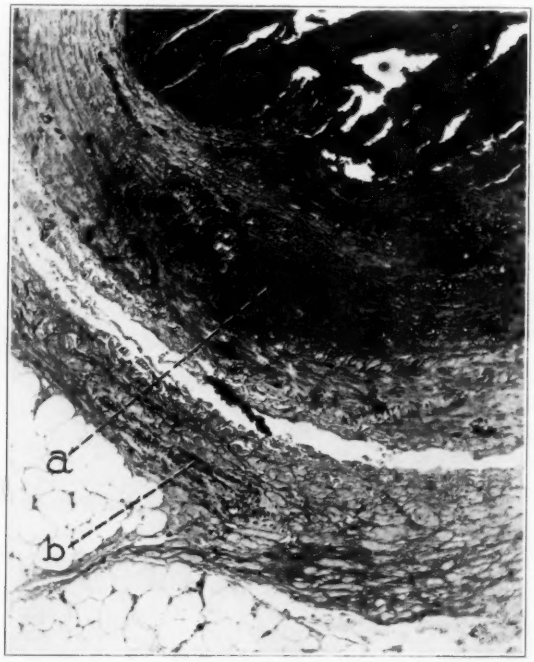

Fig. 5.—Higher magnification of a portion of the vessel illustrated in figure 4. Hemorrhage into the media (*a*) and a collection of lymphocytes (*b*) in the adventitia are seen.

A number of sections of blood vessels removed from patients at operation were cultured under similar technic and did not show a growth. In rabbits inoculated intravenously with the organism and in others inoculated subcutaneously along the marginal ear vessels, lesions did not develop even though some animals were observed for as long as eighteen months. These experiments cannot be considered conclusive, for it is difficult to produce actinomycosis in rabbits. This phase of the study, however, emphasizes the importance of carefully considering favorable evidence and applying fundamental principles even in the face of what appears to be positive evidence. We are unable at present to say with certainty whether this organism played an etiologic part in the disease in question.

The general impression obtained from study of the sections is that the condition is chronic periarteritis and arteritis. Peculiar, circumscribed areas of what appeared to be granulation tissue were present in the adventitia of the blood vessels and suggested granuloma; this represented the most characteristic lesion present (fig. 1). The Gram stain revealed minute, filamentous, gram-positive material in these areas which could easily be interpreted as being mycelia. In addition, infiltration of round cells was present in the adventitia around the vasa vasorum and to a slight extent in the media of the vessels (figs. 2 and 3). Hemorrhage was present in the media in some regions (figs. 4 and 5). The intima in many places was markedly thickened; the basal portion appeared acellular, and there were superimposed cellular layers, which indicated that the intimal proliferation had taken place in different stages. In other areas the thickened intima was uniformly cellular. In some sections a small lumen was still present, whereas in others the lumen had been completely occluded by either cellular or acellular thrombi.

Careful study of the affected arteries indicated that the lesion probably began as periarteritis of a small segment of the artery. When the artery was palpated at this stage, segments from 1 to 2 cm. in length were tender, but pulsations were still present. Tenderness was not present just proximal or just distal to the involved segment. What apparently happened was that the process subsided when it reached this stage, leaving the wall of the vessel thickened, but patent, or the process continued, spreading into the surrounding tissue as well as to the media and intima, with thrombosis of the involved segment. The history, clinical course, and pathologic appearance of the vessels did not suggest either periarteritis nodosa or thrombo-angiitis obliterans. We are inclined to believe that this is a newly described lesion.

COMMENT

The clinical pictures in these two cases are similar in many ways and seem to represent a definite clinical syndrome. The patients were admitted to the clinic because of similar symptoms. Microscopic study of sections of the blood vessels removed for biopsy disclosed identical lesions.

Actinomyces, species unidentified, had been found in pure culture from a small segment of the artery removed for biopsy from the first patient, approximately four weeks before the second patient had been admitted to the clinic. The similarity of the clinical features in these cases was so striking that a clinical diagnosis of actinomycosis of the temporal vessels was made in case 2. This seemed to be confirmed when Actinomyces was obtained in pure culture from a segment of the temporal artery. For that reason, the first patient was treated with large doses of potassium iodide for a period of four months, at which time the pain over the scalp and along the temporal vessels disappeared and did not recur for fifteen months. This patient had had no foci of infection. Marked dental sepsis, however, was present in case 2, but after all the infected teeth had been removed, the patient had remained well to the time of writing. This is of clinical interest, as Actinomyces often seem to gain entrance into the body by way of infected teeth. It is of interest to recall that in case 2 the first symptoms observed by the patient were pain around the teeth and stiffness of the jaw, followed a week later by pain over the forehead with the development of tender areas along the vessels of the scalp. The history suggests an infection of some type, with focal localization in the arteries of the scalp. The reasons why a diagnosis of actinomycosis cannot be said to have been confirmed have been stated.

From the clinical standpoint, too little is known of arteritis, and the pathologic criteria are not as yet well established. The types of arteritis which stand out as clinical entities are as follows: (1) thrombo-angiitis obliterans, which is the best known of these disease entities; the description of this by Buerger [1] and the confirmation of his work by many workers [2] have removed from the literature many diverse, heterogeneous types and have put them in one category, and (2) periarteritis nodosa,

1. Buerger, Leo: The Circulatory Disturbances of the Extremities, Including Gangrene, Vasomotor and Trophic Disorders, Philadelphia, W. B. Saunders Company, 1924.

2. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thrombo-Angiitis Obliterans: Clinical, Physiologic and Pathologic Studies, Philadelphia, W. B. Saunders Company, 1928.

or Kussmaul's disease, which was described by Kussmaul and Maier [3] in 1866, and is probably a pathologic and clinical entity. In this disease periarteritis, with acute, subacute and chronic stages, is present; in the adventitia are nodular formations composed of polymorphonuclear leukocytes and eosinophils. There is a predilection for involvement of the smaller arteries of the viscera rather than of the peripheral bed. The symptoms are largely those caused by ischemic neuritis.

Recently, Libman and Sacks [4] described certain changes in the smaller arteries in cases of verrucous or indeterminate endocarditis. However, this arteritis may occur independently of endocardial involvement. The lesion in the capillaries and arterioles indicated active proliferation and necrosis. There was occlusion by proliferative and disintegrating cells. At times, intimal granulomas were observed. Acute arteritis has been described by von Glahn and Pappenheimer [5] in rheumatic fever. This is probably a secondary form. Arterial changes, including various reactions of the arteries, have been described in many diseases, including typhoid fever, typhus fever, rheumatic fever, cholera, bacterial endocarditis and mycotic disease. There is also an ulcerative form observed in arteries contiguous to acute abscesses.

SUMMARY

Two patients, a woman aged 55 and a man aged 68, were observed at the Mayo Clinic in the spring of 1931, because of fever, weakness, anorexia, loss of weight, anemia, mild leukocytosis and painful, tender areas over the scalp and along the temporal vessels. The symptoms had been present from four to six weeks. Localized periarteritis and arteritis were present in each case. Relapses or complete remissions had occurred in both. Study of the microscopic sections of the blood vessels removed for biopsy disclosed identical lesions. Both patients apparently recovered completely from the local condition although one died approximately two years later from congestive heart failure and renal insufficiency. Results of bacteriologic studies are reported, but these are inconclusive. This report may represent a new clinical syndrome the etiology of which is still obscure.

3. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484 (March 28) 1866.

4. Libman, Emanuel, and Sacks, Benjamin: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701 (June) 1924.

5. von Glahn, W. C., and Pappenheimer, A. M.: Rheumatic Diseases of Auricle and Blood Vessels, Tr. A. Am. Physicians **43**:203, 1928.

GENERALIZED THROMBO-ANGIITIS OBLITERANS

REPORT OF A CASE WITH INVOLVEMENT OF RETINAL VESSELS AND SUPRARENAL INFARCTION

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There is a group of vascular diseases about which little is known, which frequently must be passed without recognition and which may often be submerged beneath and masked by other more obvious lesions. This is the class of generalized, nonspecific, chronic arteritis and phlebitis of which Buerger's disease undoubtedly is a type. Reports of thrombo-angiitis obliterans affecting vascular territories other than the extremities are accumulating. Barron and Lilienthal [1] attempted to direct attention to the more general distribution of the disease in contradistinction to what was previously believed concerning it—that it was a disease involving the blood vessels of the extremities exclusively. In substantiation of this hypothesis, they reported cases of their own and those from the literature. Taube [2] recently reported two cases of mesenteric involvement and collected the reports of twenty-six others which appeared in the literature and which deal with the process as it occurs in the spermatic, cerebral, carotid, aortic, coronary, mesenteric, celiac and other vessels. Barker [3] reported a case in which diffuse, nonspecific arteritis of the smaller arteries was found. There were recent thrombosis of the internal iliac veins, infarctions of the lungs and similar conditions. The essential lesions were scattered about in various organs. In the smaller arteries there was a peculiar obliterating type of endothelial proliferation of a rather striking degree without involvement of the media. No cause could be found. In all of the cases the lesions were marked and advanced. Furthermore, in all but the last they

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1. Barron, M. E., and Lilienthal, H.: Thrombo-Angiitis Obliterans: General Distribution of the Disease, Arch. Surg. **19**:735 (Oct.) 1929.

2. Taube, N.: Mesenteric Involvement in Buerger's Disease, J. A. M. A. **96**:1469 (May 2) 1931.

3. Barker, N. W.: Diffuse Arteritis of Unknown Etiology, Proc. Staff Meet., Mayo Clin. **7**:173, 1932.

were apparently uneven in their distribution and appeared to have a regional dispersal.

It is reasonable to suppose that the disease is not thought of often enough as generalized, that its manifestations have been overlooked, and that it may more frequently lie at the foundation of other entities, especially as it inherently possesses potentialities of protean modes of expression.

We report a case which presents many unusual and highly interesting features. The vascular changes, the peculiar fibrosis of the lungs, the bilateral infarction of the suprarenal glands and the alterations in the retinal vessels stand out as the most important findings. Were it not for the suprarenal insufficiency, which may be regarded as incidental, the issue would probably not have been fatal so early in the course of the disease, and the pathologic study would have been deferred to a later stage.

REPORT OF CASE

History.—C. E., a single man, aged 19, when first seen complained of intermittent pain and swelling of the legs of a year's duration. A year previously, a hard, painful swelling in the region of the left calf gradually developed. It lasted for about three weeks, necessitating rest in bed, and then it gradually subsided. For the next three months the patient was ambulatory, but did not regain his sense of well-being. Then another painful swelling, on this occasion in the region of the right calf, appeared and remained for three weeks. Six weeks before entry there was a gradual involvement of the left thigh and groin. It persisted for two weeks. About four weeks before entry the patient began to have gas pains in the lower portion of the abdomen, which became very severe; they were of a cramping, colicky nature and were accompanied by nausea and vomiting. The last two continued for three days, and the pain for three weeks. During the second week it was noted that the patient had fever, and that a slight jaundice had occurred. He entered the hospital at this time, and shortly afterward a sudden, sharp pain of a pleuritic nature developed in the right anterior region of the chest. This was followed by cough and blood-streaked sputum. During a stay of ten days in the hospital, the abdominal pain was improved, the jaundice cleared, and the cough and sputum were relieved. The patient returned home. He noticed a slight difficulty in vision on occasions during this period. Two days later he began to have pain, tenderness and swelling of the right thigh and groin. All movements of the right hip were painful. The patient returned to the hospital. He believed that he had lost about 50 pounds (22.7 Kg.) during the six weeks before entry. Except for the fact that he smoked from twenty to thirty cigarets a day, the past history and family history were noncontributory. He said that he had not had a syphilitic infection.

Physical Examination.—The patient was a fairly well developed but poorly nourished man who appeared acutely ill and complained severely of pain in the right thigh. The skin was hot, dry and flushed. Several small, discrete lymph nodes were palpated in the right posterior cervical region and several soft nodes, about 1 cm. in size, in the left groin. The conjunctivae showed a subicteric tint. The pupils were small, equal and active. The fundi showed that the arteries were very tortuous, with dilatation and streaking near the disks. The veins were

tortuous and dilated, and depressed by the crossing arteries. The cilioretinal vessels were enlarged. The lips were dry and cracked. The tongue was coated. The lungs disclosed diminished expansion at the right base, increased vocal fremitus, harsh breath sounds and no râles. The heart was not enlarged. The sounds were of poor quality. The rate was 120, and the rhythm regular. There were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The abdomen was full and symmetrical. Much gas and borborygmi were evident. There was slight voluntary guarding over the entire abdomen. There was definite tenderness just above the right inguinal ligament. The spleen, liver and kidneys were not felt. The external genitalia were normal. Rectal examination showed nothing of importance. The right leg was held in abduction, external rotation and flexion. Passive movement caused severe pain, which was maximum over the inner aspect of the thigh along the course of the saphenous vein. Palpation of this area caused pain. There was no increased redness or heat. The right leg and thigh were one-third larger than the left. The swelling was slightly pittable. The left leg appeared to be normal. Peripheral pulsations were equal and normal in all respects. The reflexes of the triceps and biceps and the radial reflexes were equal and active. The patellar reflex was absent on the left side; it was not tried on the right. The Achilles reflex was absent bilaterally.

Laboratory Examination.—Hemoglobin was 7.5 Gm. per hundred cubic centimeters of blood (54 per cent, Sahli). The red blood cells were 2,690,000; the white cells varied from 8,000 to 18,000 with from 80 to 89 per cent polymorphonuclears. The specific gravity of the urine was 1.020 on entrance. The albumin and sugar were normal. There were 1 or 2 epithelial cells and in each high power field, 2 or 3 pus cells in the sediment and from 1 to 3 hyaline casts. Many of the hyaline casts contained as many as 12 epithelial and pus cells. A few were finely granular; rarely was a coarsely granular cast found. The bile was normal. Urobilinogen was present. According to the Volhard tests, the specific gravity varied from 1.009 to 1.011. The Addis concentration test showed a cast count of 13,000 for the total volume. The red blood count was 26,000 for the total volume. The white blood cells and epithelial cells numbered 222,000 for the total volume. The clearance test for urea and the phenolsulphonphthalein test showed nothing abnormal. The sedimentation time was seventeen minutes. Retractility of the clot was normal. All other tests, including the Wassermann test, were negative, and blood cultures showed nothing abnormal.

Roentgen studies revealed increased density in the outer lower part of the right upper lobe. A roentgenogram of the chest taken eighteen days later revealed an additional change in the form of a spherical shadow which was interpreted as a small cavity.

The diagnosis most often suggested was multiple thrombophlebitis on an infectious basis. An unusual form of thrombo-angiitis obliterans was mentioned on the first day of hospitalization.

Course.—The temperature on entry was 39.2 C. (102.5 F.), but on the next day it dropped to 37.8 C. (100 F.) and the patient felt much better. For the first eight days the patient seemed to improve, the temperature remaining below 37.5 C. (99.5 F.) and the abdominal complaints being relieved. The pain and the swelling of the right thigh gradually improved, and the patient was able to move the leg freely without feeling discomfort. On the eighth day he complained of a dull, aching pain at the margin of the left rib in the midaxillary line. There was no guarding of the left upper quadrant, but on deep palpation the patient complained of tenderness. The spleen was not felt. On the tenth day the fever

began to rise and gradually reached a level of around 39 C. (102.2 F.), where it remained until death. The patient became irritable and complained a great deal. On the fourteenth day spontaneous thrombosis of the right antecubital vein occurred. On the fifteenth day in the hospital, signs of meningeal irritation developed. A lumbar puncture was performed, and the findings were negative. This suggested meningismus. The patient continued to lose ground. On the nineteenth day the blood pressure was 100 systolic and 60 diastolic. On the twentieth day the patient became comatose. A transfusion of 300 cc. of whole blood was given without benefit. On the twenty-first day the coma became deeper, and the patient died of heart failure.

Postmortem Examination.—Postmortem examination was performed one hour after death. The lungs lay in the normal positions. The right pleural cavity was obliterated posteriorly over the lower lobe and inferiorly by adhesions between

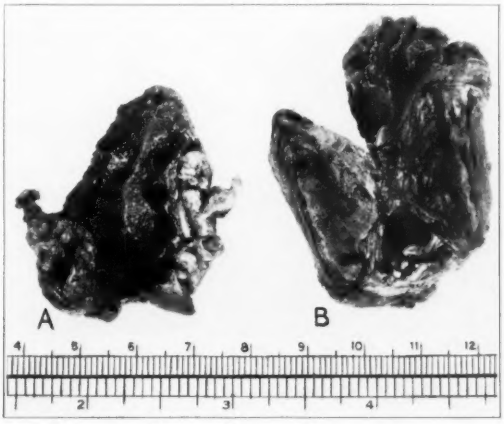

Fig. 1.—The suprarenal glands. *A* represents the right gland; *B*, the left.

the parietal, visceral and diaphragmatic layers. The posterior adhesions were rather recent and could be easily broken by the examining finger. The adhesions on the lower portion of the lobe were much more firm and dense. On the surface of the upper part of the right lower lobe was a rectangular area which measured about 4 by 4 cm., over which the pleura was roughened and covered with fine adhesions. Deep in this area there appeared an infarcted block of pulmonary tissue in which there was a rounded, brownish, necrotic plug. Above this there was a small, empty cavity which measured about 1 cm. in diameter. The lungs felt rather firm and did not seem so creptitant or so elastic as normally. Examination of the heart revealed nothing unusual. The left suprarenal gland was perhaps three or four times as large as normal. It weighed 29 Gm. Its cortex was thinned to the extent of remaining as only a shell. Its medulla was destroyed and replaced by firm, reddish-brown, hemorrhagic material. The right suprarenal gland was smaller than the left, and weighed 17 Gm. It presented a picture not unlike that of the left side except that here the infarction was recent, and the medullarly portion was filled with a red, friable hemorrhagic coagulum and was partly cavitated (fig. 1). The aorta was smooth and elastic. It con-

tained rare, early atheromatous plaques. The saphenous vein in the right leg was found to have thickened walls and to contain an antemortem organizing thrombus. It was readily pulled from its sheath. The smaller arteries throughout the body appeared grossly to have thickened walls, and close examination revealed that minute thrombi filled the lumens of a few. This held true for most of the vessels examined, including those at the hilus of the liver, the kidney, the spleen, the branches of the gastric and pancreatic arteries, the prostatic vessels and the basilar cerebral vessels. Sections were taken from all of the vessels for microscopic examination.

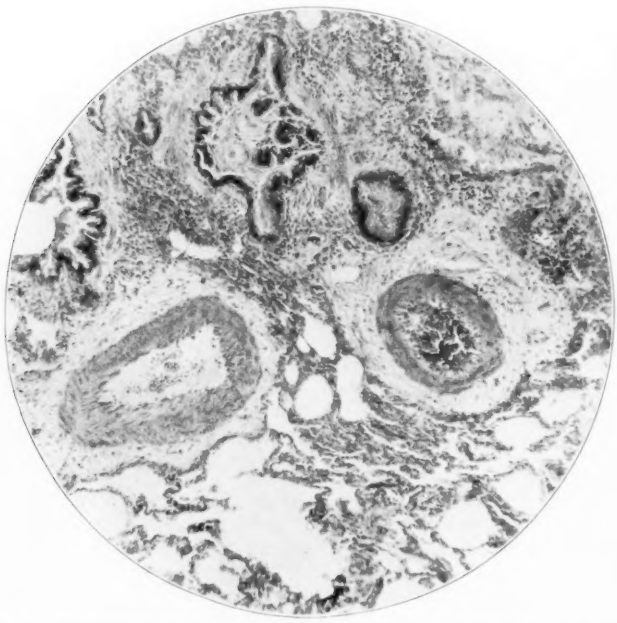

Fig. 2.—Microscopic section of the lung. Note the peribronchial and perivascular fibrosis. The vascular changes found elsewhere are seen here, with thrombosis. The increase in the connective tissue in the alveolar septums is seen.

Microscopic Examination.—Sections were studied from nine blocks of tissue removed from various parts of the lungs. The alveolar walls were found to contain an increased amount of connective tissue. They were thickened and stiffened because of the fibrosis. About most of the bronchi and blood vessels were collars of fibrous tissue through which broad, cicatricial bands were occasionally observed to course. The blood vessels displayed striking alterations, to be described (fig. 2). The infarcted areas contained degenerating or necrotic centers in which the faint shadows of the original pulmonary architecture could still be perceived. Surrounding the regions was a dense, fibroblastic border. Hemorrhage was frequently seen and in places was undergoing organization. The

alveoli throughout the lungs held numerous large endothelial cells which contained granules of brown pigment. There was no evidence of either a pneumonic or a tuberculous process. The myocardium showed early degenerative changes marked by fatty infiltration, fraying of the fibers and loss of transverse striation. No Aschoff bodies were found. Sections of the liver were punctuated throughout with small areas of focal necrosis. They showed moderate passive congestion. The mesenteric lymph nodes displayed a rather marked degree of follicular hyper-

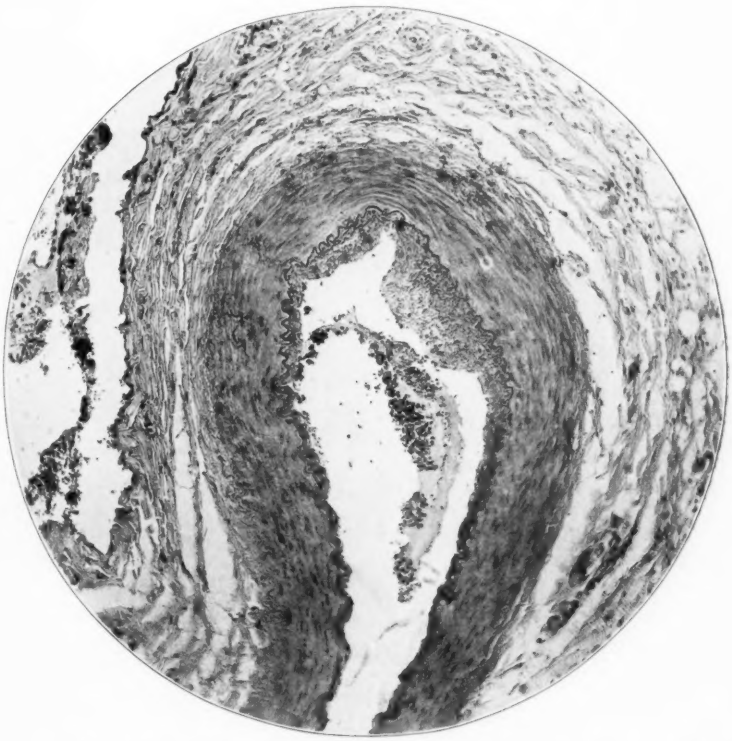

Fig. 3.—A branch of the coronary artery, showing especially the intimal thickening.

plasia. The suprarenal glands presented striking changes. Their capsules were increased in thickness in an irregular manner with an increase in connective tissue and considerable fatty infiltration. Occasional foreign body giant cells were seen in clusters external to the parenchyma. There was some lymphocytic infiltration. The right suprarenal gland was filled with recent hemorrhage. The medulla was entirely destroyed, and only occasional patches of the glomerular stratum or the uppermost cells of the vesicular portion were seen. The process on the left seemed to be older and was in the nature of an anemic infarct with

the suprarenal substance represented by the shadows of the original architecture In the pituitary gland there was apparently an increase in the number of basophilic cells throughout. In the central portion of the pars distalis was a circumscribed area occupying about three fourths of a low power field which was composed entirely of groups of cells of the basophilic type. It was not encapsulated and may have been a miliary area of hyperplasia rather than a true adenoma. In all of the smaller arteries as well as in some of the veins there were pathologic

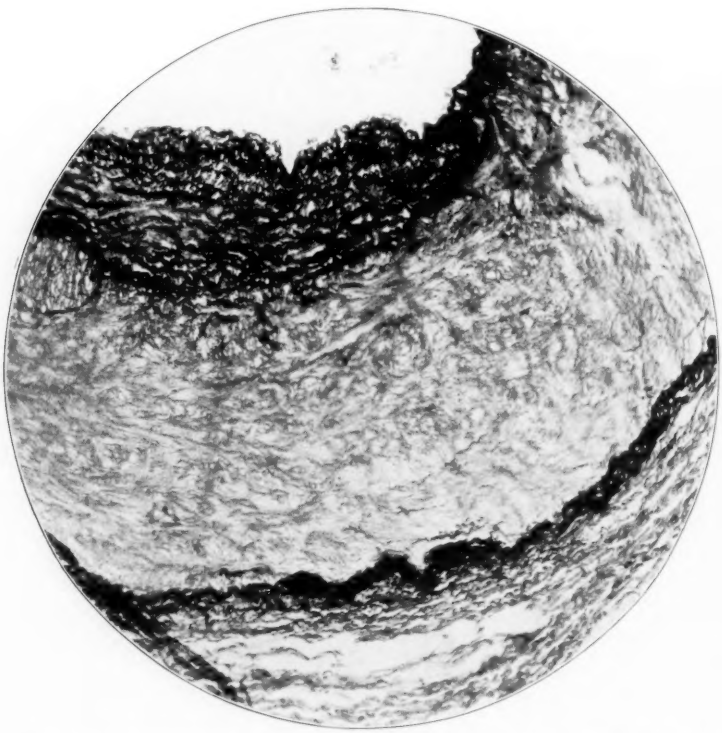

Fig. 4.—A branch of the pancreaticoduodenal artery. Note the marked reduplication of the internal elastic lamina. Weigert's elastic tissue stain; × 450.

changes (figs. 2, 3, 4 and 5). The small arteries were particularly affected. The very smallest vessels, except those distal to an actual thrombus, did not appear to be involved, nor was the aorta or most of its major branches. The adventitia showed an increased amount of connective tissue which extended in many places into the surrounding tissue. Occasionally small groups of lymphocytes or plasma cells were caught in it, suggesting a more active process at an earlier time. The fibrosis at times reached adjacent epineuria and included the neighboring veins. For the most part, however, it was confined to merely an adventitial thickening. The media contained rare plasma cells. The muscle was well preserved, although

it was somewhat hyperplastic. There was no increase in the connective tissue or fibrous replacement of the muscularis. The intima was the site of a proliferative process, and had undergone hyperplasia in an irregular manner so that it encroached on the lumen and narrowed it considerably. The proliferation did not progress to the point of actual obliteration but seemed to pave the way for the formation of a thrombus which was found in many places. The cells of the intima had a circumferential distribution. There was occasional vacuolation or a foamy appearance. The internal lamina (fig. 4) was moderately increased.

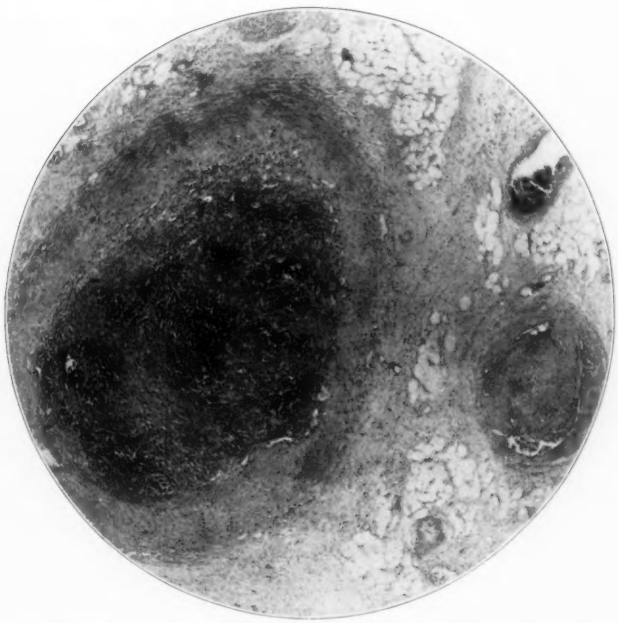

Fig. 5.—Vessels in the region of the urinary vesicle, neck and prostate. Obliterating thrombosis is present in both vascular channels. Hematoxylin and eosin stain; × 100.

The elastic fibers were reduplicated and concentric. Most of the thrombi had advanced to a stage of organization and canalization. Sections of the saphenous vein showed panphlebitis with organizing thrombosis.

COMMENT

The pathologic process in the vessels is perhaps the basic finding. For the time, the condition must be regarded as of obscure etiology. In reviewing the pathologic histology of the vessels, one must consider the various lesions affecting the circulatory system in a like manner. Among these may be mentioned the endarteritis obliterans of Virchow,

thrombophlebitis migrans, syphilitic arteritis (including Heubner's endarteritis), thrombo-angiitis obliterans, rheumatic angiitis and periarteritis nodosa. Just as most of the conditions have many points in common, so does the process under consideration resemble and differ from each of these conditions in one or more respects. As may be seen from the microscopic description, if one is to employ a descriptive diagnosis, one is forced to choose thrombo-angiitis obliterans, as only this term adequately covers the principal elements of the vascular lesions.

The periarterial, early lymphatic infiltration and the later thickening and fibrosis of the adventitia which tend to mat the neighboring nerve and vein to the artery are as a rule marked in thrombo-angiitis obliterans.[4] In this case, however, although the fibrosis was universal and occasionally included groups of lymphocytes and plasma cells, it was only of moderate degree. The venous sheaths and perineuria were only rarely reached, and then not to an extent which could have been noted grossly. The media of the vessels in this case showed the least changes. Aside from the fact that it was thickened, it was not remarkable, nor was the increase in thickness accomplished by fibroblastic proliferation but rather by an apparent muscular hypertrophy. In thrombo-angiitis obliterans there is usually an increase in the connective tissue of the media; in periarteritis nodosa, necrosis, fibrosis and hyalinization; in rheumatic arteritis, vacuolation and death of the muscle, and so on. No attempt at formation of a collateral circulation through the vasa vasorum in the media such as is discovered in some of these conditions was noted here. Except for the marked thrombus formation found in this case before the lumen had been narrowed to any considerable degree, the intimal changes are strongly reminiscent of endarteritis obliterans.

Warthin [4b] described changes in the smaller arteries in a case of syphilis in which there was thickening of the intima with hyaline changes but without infiltration and in which no spirochetes were found. He observed that the vessels became concentrically thickened through proliferation, and that the lumen was obliterated by fibroblastic tissues. This was especially well noted in the vasa vasorum of the aorta. Heubner described these alterations, especially in the central nervous system. In our case there is no evidence of a syphilitic process, and it is particularly to be observed that the large vessels are spared. It is the smaller arteries and not the very small nor the major channels which are involved.

4. (*a*) Brown, G. E., and Allen, E. V.: Thrombo-Angiitis Obliterans, Clinical, Physiologic and Pathologic Studies, Collaborating in Pathology with H. R. Mahorner, Philadelphia, W. B. Saunders Company, 1926. (*b*) Warthin, A. S.: Syphilis of Medium and Smaller Arteries, New York M. J. **115**:69, 1922.

The condition known as thrombo-phlebitis migrans has found its way into recent literature, especially on the continent and in England.[5] Little pathologic study has been accorded it. It usually appears in small lengths of the superficial peripheral veins and frequently in the lungs and the abdomen. The heart and the brain are more rarely affected. The disease is characterized by a long course with frequent febrile exacerbations. Since the prognosis is favorable and not more than a score of cases are reported, the opportunity for study at autopsy is infrequent. The cases reported by Moorehead, Abrahamson, Eyle, Ellison and others were, as the name suggests, principally evidenced in the veins and did not clinically point to the arterial tree, as in our case.

The lesion in the lung is of itself unusual. It is, no doubt, to be explained on a circulatory basis dependent on a pulmonary oligemia and on actual infarction due to thrombosis of the arteries. In 1929, Frothingham[6] reported a case similar in many respects, so far as the lungs are concerned, to our case. Extensive fibrosis of the alveolar septums, many of which were almost avascular, a peculiar peribronchial and perivascular increase in connective tissue, thrombosis of the smaller arteries and infarctions of the lungs were found. Many other cases of nonspecific pulmonary fibrosis have been reported, such as the eighteen cases reported by Posselt[7] and those of Schütte[7] and of Eppinger and Wagner.[7] For the most part, the larger arteries showed involvement, too, as in Ayerza's disease, but some of the lesions were confined to the smaller vessels in the lungs, except in Frothingham's case, in which thromboses were present in the uterine and vaginal vessels. No mention was made of the presence or absence of vascular changes elsewhere in the body in vessels of the same size.

Because the clinical manifestations in this case were so widespread, it would be well to try to correlate them with the pathologic findings. The painful swellings in the calves of which the patient first complained were undoubtedly due to thrombophlebitis of the veins of the lower extremity. The severe attack of cramplike abdominal pain, nausea and vomiting was probably a result of the involvement of mesenteric vessels with the resulting ischemia of the bowel. The icterus was no doubt on a basis of hepatic focal necrosis which may have been a result of the involvement of the hepatic vessels. The pleuritic pain followed by cough and hemoptysis is related to the pulmonary thrombosis. Barker[8]

5. Barber, H.: Thrombo-Phlebitis Migrans, Brit. M. J. **1**:281 (Feb. 13) 1932. Moorehead, T. G., and Abrahamson, L.: Thrombo-Phlebitis Migrans, Brit. M. J. **1**:586 (April 7) 1928.

6. Frothingham, C.: A Case of Bilateral Progressive Thrombosis of the Smaller Branches of the Pulmonary Arteries, Am. J. Path. **5**:11, 1929.

7. Quoted by Frothingham.[6]

8. Barker, N. W.: Thrombo-Angiitis Obliterans with Occlusion of Both Femoral Veins and Both Popliteal Arteries, M. Clin. North America **15**:233, 1931.

described a case with pulmonary embolism in a patient with thrombo-angiitis obliterans. The difficulty of vision in our case was probably due to the involvement of the retinal vessels. The fever and the evidence of peritoneal irritation followed by the prostration which the patient suffered during the last few days of life were undoubtedly due to suprarenal infarction.[9] Fever has been found to be an almost constant feature of suprarenal apoplexy. The clinical features of epigastric pain and tenderness followed by prostration and feebleness of the pulse terminating in death fit in well with Lavenson's [10] peritoneal type of suprarenal hemorrhage. He and others found that this was the most common type of reaction found in this rare condition.

The urinary findings and the results of the tests of renal function are of interest. On entry the specific gravity of the urine was 1.020. Later there was inability to concentrate above 1.011. The urea clearance and phenolsulphonphthalein tests were within normal limits. However, there was a definite increase in casts as determined by the Addis concentration test. Many of these casts were remarkably cellular, and as many as 12 cells were found in some of them. These changes are probably due to the involvement of the smaller arteries of the kidney. It is interesting to speculate on the future progress of these changes in the kidneys had the patient not died. Because of the wide extent of the renal arteriolar involvement, further degrees of renal insufficiency would most probably have occurred. The marked meningismus and terminal external strabismus must have been due to the involvement of the cerebral vessels. Nervous symptoms such as convulsions, coma and typhoid states, following suprarenal apoplexy have been described by Lavenson, but meningismus has not been mentioned as a manifestation of suprarenal apoplexy. The prolonged clotting time is of interest, since Steel [11] believed that the coagulation time was shortened in this condition. Secondary anemia has been found by Brown [4a] to occur in the more fulminant types of thrombo-angiitis obliterans. Leukocytosis is an unusual finding without secondary infection. The rapid sedimentation time may indicate that an infectious process of some type is the cause.

The hemorrhagic infarction of the suprarenal glands may no doubt be explained on a thrombotic basis. Just why the suprarenal glands (or the lungs, for that matter) should have been chosen, it is difficult to say. However, it is to be noted that there was an uneven degree of

9. Seligman, B.: Suprarenal Hemorrhage in the Adult, M. J. & Rec. **135**: 209 (March 2) 1932.

10. Lavenson, R. S.: Acute Insufficiency of the Adrenals, Arch. Int. Med. **2**:62 (Aug.) 1908.

11. Steel, W. A.: Intravenous Citrate of Soda Treatment of Thrombo-Angiitis Obliterans, M. Rec. **99**:370, 1921.

involvement throughout the vascular tree. According to Goldzieher,[12] if the larger medullary vein or central veins of the suprarenal glands are thrombosed, hemorrhagic infarction is inevitable. This has been studied experimentally by Martinotti and Torrini,[13] who ligated the central vein. In less than twenty-four hours they found marked alteration in the cortical cells, the changes in those of the medulla being less striking. It is interesting to note in this connection that Torrini found that unilateral ligation of the central vein which is followed by stasis, thrombosis and hemorrhagic infarction on the side on which the ligature has been applied frequently gives rise to a similar process on the opposite side, which has not been touched. The mechanism of this sympathetic infarction may be explained on a similar basis. The difference in age in the suprarenal changes found in our case are compatible with such an explanation. Of course hemorrhage and infarction of the suprarenal glands may occur in a score of conditions, such as trauma, severe venous congestion and generalized infection or intoxication, but it is not necessary to postulate such a basis in this case. We have been unable to find another case of suprarenal apoplexy resulting from thrombo-angiitis of the suprarenal vessels.

Brasser,[14] however, described a case of suprarenal apoplexy in which there was an old thrombosis of the saphenous vein, and he thought that a constitutional defect in the blood vessels might have predisposed to the thrombosis in his case. Brasser, Bittorf,[15] Simmonds[16] and Pearl and Brunn[17] also described cases in which there was evidence of thrombosis elsewhere in the body. In none of these cases, however, was there evidence of thrombo-angiitis obliterans.

The changes in the retinal vessels are of particular importance from a clinical standpoint, as they are the only ones that can be seen and therefore offer an important clue to the diagnosis. Our patient complained of slight difficulty in vision, which probably resulted from these changes. Grasser[18] described involvement of the retinal vessels in a typical case of Buerger's disease in which there was complete loss of

12. Goldzieher, N. A.: The Adrenals: Their Physiology, Pathology and Diseases, New York, The Macmillan Company, 1929.

13. Martinotti and Torrini, quoted by Goldzieher.[12]

14. Brasser, A.: Beitrag zur Kenntnis der Nebennierenerkrankungen, Klin. Wchnschr. **3**:738, 1924.

15. Bittorf, A.: Zur Kenntnis der Nebennierenerkrankungen, München. med. Wchnschr. **73**:1928, 1926.

16. Simmonds, M.: Ueber Nebennierenblutungen, Virchows Arch. f. path. Anat. **170**:242, 1902.

17. Pearl, F., and Brunn, H.: Suprarenal Apoplexy, Bilateral, Surg., Gynec. & Obst. **47**:393, 1928.

18. Grasser, E. B.: Partial Occlusion of the Retinal Vessels in Thrombo-Angiitis Obliterans, Am. J. Ophth. **15**:235, 1932.

vision. The ophthalmologic examination revealed conditions similar to those found in this case. Changes in the retinal vessels have been found in other generalized vascular diseases, such as periarteritis nodosa, Raynaud's disease and arteriosclerosis. The alterations in the latter conditions are known and can be easily differentiated from those described in this case. In periarteritis nodosa, aneurysmal dilatations of the retinal arteries have been described. In Raynaud's disease spasm of the retinal arteries has occasionally been noted. In arteriosclerosis, the retina is often involved, the changes in the veins are not so marked, and there is not so much dilatation of the vessels as there was in this case.

SUMMARY

1. An unusual case of generalized vascular disease, probably early thrombo-angiitis obliterans, in which autopsy was possible early in the course because of the involvement of vital structures (the suprarenal glands) is reported.

2. Involvement of the cerebral, retinal, pulmonary, coronary, mesenteric, suprarenal, pancreatic, duodenal, hepatic, renal and prostatic vessels and of the vessels of the extremities was found. The clinical manifestations of the changes and of the suprarenal apoplexy in this case are discussed.

3. The possibility that thrombo-angiitis obliterans is more frequently a generalized disease is pointed out.

RELATION OF THE PLASMA CHOLESTEROL TO OBESITY AND TO SOME OF THE COMPLICATING DEGENERATIVE DISEASES

(DIABETES MELLITUS, ESSENTIAL HYPERTENSION, OSTEO-ARTHRITIS AND ARTERIOSCLEROSIS)

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AND
CHARLES A. POINDEXTER, M.D.*
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Studies of the cholesterol content of the plasma in the obese and the influence that several associated clinical conditions have on it are reported in this paper. It is important to know whether the excessive indulgence in food by human beings over a long period is associated with a rise in the cholesterol content of the blood. The relation between obesity and essential hypertension, diabetes mellitus and arteriosclerosis has been stressed for many years; the increased blood cholesterol in the latter three diseases has been frequently observed by many workers. Because of these facts, a critical investigation of the relationship between the blood cholesterol and the body weight and the degenerative diseases supposedly resulting from obesity suggested itself. Oddly enough, we were unable to find a single study in the literature in which these aspects of the subject were investigated; the published records given herewith were usually part of a related problem.

LITERATURE

Denis[1] stated that the plasma cholesterol is elevated in cases of obesity; she remarked, however, that each of the two subjects in her normal group who had the greatest weight showed a low plasma cholesterol. Epstein and Lande[2] believed obesity to be one of the condi-

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* Oliver Rea Fellow in Medicine.

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From the Department of Medicine, New York Post-Graduate Medical School and Hospital.

1. Denis, W.: Cholesterol in Human Blood Under Pathological Conditions, J. Biol. Chem. **29**:93, 1917.

2. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: I. The Relation of Cholesterol and Protein Deficiency to the Basal Metabolism, Arch. Int. Med. **30**:563 (Nov.) 1922.

tions associated with a high blood cholesterol. Labbé and Heitz [3] reported six cases of obesity with an associated hypercholesteremia. Weil, Guillaumin and Abricosoff [4] studied twenty-four obese subjects; sixteen showed a high blood cholesterol, and eight, normal values. Koning [5] reported ten cases of obesity, in each of which there was a distinctly elevated blood cholesterol. It should be stated that the obese subjects studied by Weil and his co-workers and by Koning usually had an associated disease, such as hypertension, arthritis, gout and diabetes mellitus. Waldorp [6] and Petersen and Levinson [7] recorded cases of obesity complicated by hypertension or endocrine dysfunction in which the plasma cholesterol was moderately elevated.

White and Hunt [8] stated that overnutrition in the diabetic child is associated with a high plasma cholesterol. Bing and Heckscher [9] studied five cases of obesity and found that the blood fat was greatly increased (twice the upper normal limit). Likewise, Gray [10] showed that diabetic patients who were overweight or near the normal weight had a tendency toward elevated blood fat.

Bonnefous and Valdiqué [11] and Laurentier and Valdiqué [12] found that the cholesterol content of the blood was consistently elevated in ten cases of lipomatosis. Strauss and Schubardt [13] reported cholesterol studies in one hundred and sixty patients with various diseases; one case of lipomatosis showed an elevated blood cholesterol.

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3. Labbé, M., and Heitz, J.: La cholestérinémie des diabétiques, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1546, 1924.

4. Weil, M. P.; Guillaumin, C. O., and Abricosoff, L.: Contribution à l'étude du sang des obèses, l'état de pléthore, Ann. de méd. **23**:328, 1928.

5. Koning, J. W.: Het cholestearine-gehalte van het bloed bij verschillende ziekten, Nederl. tijdschr. v. geneesk. **66**:540, 1922.

6. Waldorp, C. P.: Relaciones entre la hipertensión arterial primitiva (genuina o esencial), enfermedades de la nutrición y sistema endócrinovegetativo, Semana méd. **35**:609, 1928.

7. Petersen, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of Normal Men and of Clinical Patients: III. Detailed Study of the "Normal" Group and of Miscellaneous Clinical Patients, Arch. Path. **9**:198 (Jan.) 1930.

8. White, P., and Hunt, H.: Cholesterol of the Blood of Diabetic Children, New England J. Med. **202**:607, 1930.

9. Bing, H. I., and Heckscher, H.: Untersuchungen über Lipämie: III. Pathologische Verschiebungen der Blutfettmenge, Biochem. Ztschr. **149**:90, 1924.

10. Gray, H.: Lipoids in 1,000 Diabetic Bloods with Special Regard to Prognosis, Am. J. M. Sc. **168**:35, 1924.

11. Bonnefous, R., and Valdiqué, A.: Hypercholestérinémie et lipomatose, Ann. de dermat. et syph. **5**:290, 1924.

12. Laurentier, C., and Valdiqué, A.: Lipomatose et hypercholestérinémie, Ann. de dermat. et syph. **8**:297, 1927.

13. Strauss, H., and Schubardt, W.: Ueber den Cholesteringehalt des Blutserums, Zentralbl. f. inn. Med. **43**:425, 1922.

On the other hand, several studies have been recorded in the literature in which the blood cholesterol in obese subjects was found to be normal or low. Blix [14] studied five cases in which there was a normal cholesterol value; he emphasized the fact that when an elevated cholesterol is found in an obese subject, an underlying disease, such as an endocrine imbalance, may be responsible for the hypercholesteremia. Rony and Levy [15] reported the results for eighteen obese and fifteen normal subjects; the blood cholesterol averaged 128 mg. per hundred cubic centimeters in the obese and 132 mg. in the normal patients. In a personal communication to Gray,[10] Luden stated that one case of obesity (390 pounds [177 Kg.]) which she studied showed a blood cholesterol of 130 mg.

MATERIAL AND METHODS

The material for this study was obtained from the clinic for obesity of the outpatient department of the New York Post-Graduate Hospital. Single studies of the blood were made on the day the patients were admitted to the clinic. In every case the blood was taken in the morning; in most instances the patients had previously eaten their customary breakfasts.

The experimental and statistical data to be described are based on ninety-four obese persons who were overweight 20 per cent or more. The ideal weights were obtained from the height-weight tables furnished by Joslin.[16]

We classified our subjects into four groups:

Group I was composed of fifty-three subjects who showed so-called uncomplicated (frank, exogenous) obesity; that is, though distinctly overweight, they showed none of the stigmas of endocrine dysfunction and gave no history or clinical evidence of nephritis, hypertension, diabetes mellitus or arteriosclerosis.

Group II was composed of twenty-five subjects. In these, the obesity was complicated by what may be termed metabolic disorders, namely, essential hypertension, arteriosclerosis and diabetes mellitus. In this class were included all subjects showing a definitely diminished tolerance to ingested carbohydrate as determined by the dextrose tolerance curve, even though signs and symptoms of diabetes mellitus were lacking (the prediabetic state).

Group III was composed of eleven patients in whom obesity was complicated by arthritic manifestations (rheumatoid arthritis and osteo-

14. Blix, G.: Studies on Diabetic Lipemia, Acta med. Scandinav. **64**:142, 1926.

15. Rony, H. R., and Levy, A. J.: Studies on Fat Metabolism: I. Fat Tolerance in Obesity. A Preliminary Study, J. Lab. & Clin. Med. **15**:221, 1929.

16. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 967.

arthritis). We deemed it advisable to place these subjects in a separate group, since a study of their plasma cholesterol values showed rather odd results.

Group IV was composed of five patients in whom obesity was complicated (or caused) by definite endocrine dysfunctions (in this series, ovary, thyroid and pituitary dysfunction). Table 1 gives the distribution of the ninety-four cases according to the sex, age and the various groups as previously outlined according to the percentage of overweight.

It is necessary to determine the limits of normality for the cholesterol content of the blood. Rothschild and Wilensky [17] and Weidman and Sunderman [18] reviewed the cholesterol values arrived at by earlier

TABLE 1.—*Distribution (Sex, Age and Groups) According to the Percentage of Overweight in Ninety-Four Cases of Complicated and Uncomplicated Obesity*

Overweight, per Cent	Sex		Average Age, Years (Both Sexes)	Number of Cases of Obesity				
	Male	Female		Uncomplicated	Complicated by Metabolic Diseases	Complicated by Arthritis	Complicated by Endocrine Diseases	Total
20-30	2	18	44.5	10	6	4	..	20
30-40	..	20	40.6	9	8	3	..	20
40-50	1	15	38.7	10	4	2	..	16
50-60	..	12	33.9	9	..	2	1	12
60-70	1	13	38.7	7	4	..	3	14
70-80	..	5	38.6	3	1	..	1	5
80-90	..	3	37.3	3	..	..	..	3
90-100	..	..	....	..	..	..	..	..
100+	..	4	35.0	2	2	..	..	4
Total	4	90	....	53	25	11	5	94

observations. The results obtained with the newer methods (the method of Bloor, Pelkan and Allen [19] and recent modifications) were uniformly higher than those obtained with the older procedures. Bloor [20] found that the average cholesterol content of the blood for normal men is 210 mg., and for normal women, 230 mg., but Gorham and Myers [21]

17. Rothschild, M. A., and Wilensky, A. O.: Studies in Cholelithiasis: I. The Disturbances of the Cholesterin Metabolism as a Factor in Gall-Stone Formation, Am. J. M. Sc. **156**:239, 1918.

18. Weidman, F. D., and Sunderman, F. W.: Hypercholesterolemia: I. The Normal Blood Cholesterol Figures for Man and for the Lower Animals, Arch. Derm. & Syph. **12**:679 (Nov.) 1925.

19. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**: 191, 1922.

20. Bloor, W. R.: The Distribution of the Lipoids ("Fat") in Human Blood, J. Biol. Chem. **25**:577, 1916.

21. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, Arch. Int. Med. **20**:599 (Oct.) 1917.

entertained the belief that these figures are too high, and that values ranging between 160 and 170 mg. are more nearly correct. The latter figures are close to the normal values for blood cholesterol accepted by Rabinowitch.[22] Hunt,[23] however, gave the upper limit of normal as 230 mg. According to the modified Bloor method employed in this laboratory over a period of almost three years (method of Sackett [24]), we are inclined to accept the higher values for normality. In fact, we have observed normal fasting subjects with values for plasma cholesterol distinctly above 230 mg. but rarely higher than 250 mg. In our hands, Sackett's method [24] modified by the temperature control procedure used in this laboratory [25] (the method used in this investigation) leads us to believe that the range of plasma cholesterol in normal subjects lies between 160 and 230 mg.; values from 230 to 250 mg. are only suggestive of hypercholesteremia; figures above 250 mg. are considered to be definitely elevated (hypercholesteremia), and those below 160 mg. to be distinctly below the normal level (hypocholesteremia). We have expressed this view elsewhere.[26]

The standard deviation as determined for each group was calculated from the formula

$$\mu = \sqrt{\frac{\Sigma(d^2)}{n}}$$

$\Sigma(d^2)$ represents the summation of the squares of the individual deviations from the mean, and n, the number of determinations.

RESULTS

Table 2 shows the results obtained in fifty-three subjects with uncomplicated obesity. The cases are arranged according to the increasing percentage of overweight; the associated clinical conditions considered as materially without influence on the cholesterol content of the plasma are indicated.

In thirty-five cases (66 per cent), the plasma cholesterol was within normal limits; twelve patients (23 per cent) showed hypocholesteremia

22. Rabinowitch, I. M.: The Cholesterol Content of the Blood Plasma in Diabetes Mellitus, Arch. Int. Med. **43**:363 (March) 1929; Observations on the Significance of the Cholesterol Content of the Blood Plasma in Diabetes Mellitus, Canad. M. A. J. **28**:162, 1933.

23. Hunt, H. M.: Cholesterol in the Blood of Diabetics Treated at the New England Deaconess Hospital, New England J. Med. **201**:659, 1929.

24. Sackett, G. E.: Modification of Bloor's Method for Determination of Cholesterol in Whole Blood or Blood Serum, J. Biol. Chem. **64**:203, 1925.

25. Mirsky, I. A., and Bruger, M.: A Note on the Liebermann-Burchard Color Reaction for Cholesterol, J. Lab. & Clin. Med. **18**:304, 1932.

26. Ashe, B. I., and Bruger, M.: The Cholesterol Content of the Plasma in Chronic Nephritis and Retention Uremia, Am. J. M. Sc. **186**:670, 1933.

TABLE 2.—*Cholesterol Content of the Plasma in Fifty-Three Cases of Uncomplicated Obesity* *

Case	Age	Sex	Weight, Lbs.	Ideal Weight, Lbs.	Overweight, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Associated Clinical Conditions
1	38	F	162	134	20.9	219	
2	48	F	164	133	23.3	229	Early myocardial insufficiency
3	35	F	163	131	24.4	193	Chronic salpingitis; ovarian cyst
4	29	M	190	152	25.0	207	
5	39	F	164	131	25.1	214	
6	34	F	181	144	25.7	174	
7	30	F	160	127	26.0	201	Chronic cervicitis; rectal ulcers
8	40	F	168	133	26.3	194	
9	63	M	177	140	26.4	276	Paroxysmal tachycardia
10	49	F	172	135	27.4	238	Varicose veins; atrophic rhinitis; chronic otitis media; furunculosis (face)
11	25	F	159	122	30.3	242	
12	32	F	160	123	30.9	176	
13	22	F	158	119	32.8	136	Subcoccygeal fistula
14	54	F	194	146	32.9	202	
15	29	F	164	123	33.3	168	
16	44	F	182	136	33.8	262	Varicose veins
17	36	F	181	135	34.0	327	
18	28	F	191	139	37.4	136	Chronic cholecystitis
19	52	F	189	137	38.0	192	
20	51	F	187	133	40.6	172	
21	43	F	211	150	40.6	149	Endometritis; chronic salpingitis; varicose veins
22	35	F	183	128	43.0	216	
23	23	F	172	120	43.3	179	
24	37	F	195	136	43.4	226	Varicose veins
25	31	F	173	119	45.3	147	Chronic cystitis
26	41	M	265	181	46.4	147	
27	38	F	197	133	48.1	192	Functional amenorrhea
28	42	F	203	136	49.3	154	
29	42	F	187	125	49.6	207	Varicose veins
30	33	F	203	133	52.6	268	
31	39	F	218	141	54.6	169	Uterine fibroid
32	34	F	231	148	56.0	216	Varicose veins
33	23	F	203	130	56.2	162	
34	32	F	197	125	57.6	136	
35	40	F	197	125	57.6	180	
36	25	F	197	124	58.8	119	Chronic cystitis
37	25	F	216	136	58.8	183	Rheumatic heart disease
38	25	F	209	131	59.5	206	Rheumatic heart disease; mitral stenosis
39	35	F	216	135	60.0	160	Varicose veins
40	55	F	223	139	60.4	255	
41	32	F	193	120	60.8	194	
42	39	F	220	136	61.8	158	Varicose veins; ventral hernia
43	36	F	195	119	63.9	133	Hemorrhoids
44	20	F	213	128	66.4	127	
45	36	F	224	133	68.4	148	Chronic endocervicitis
46	27	F	205	119	72.3	259	
47	47	F	241	138	74.6	183	
48	39	F	233	133	76.0	219	Traumatic periostitis
49	30	F	224	124	80.7	214	
50	42	F	289	159	81.7	189	
51	40	F	254	139	82.7	236	
52	35	F	270	132	102.2	193	
53	21	F	292	141	107.0	186	Vaginitis; cervicitis
Average						194 ± 43 mg. of cholesterol per 100 cc. plasma	

* The term uncomplicated obesity is used in this study to denote the absence of metabolic, arthritic and endocrine disturbances.

(below 160 mg.), and six (11 per cent), definite hypercholesteremia (above 250 mg.). The highest cholesterol value observed in this group was 327 mg. (case 17); the lowest, 119 mg. (case 36). It is interesting to note the normal or low plasma cholesterol often observed in the

TABLE 3.—*Cholesterol Content of the Plasma in Twenty-Five Cases of Obesity Complicated by Metabolic Diseases (Diabetes Mellitus, Including the Prediabetic State; Essential Hypertension, and Arteriosclerosis)*

Case	Age	Sex	Weight, Lbs.	Ideal Weight, Lbs.	Over-weight, per Cent	Plasma Choles-terol, Mg. per 100 Cc.	Associated Clinical Conditions
54	50	F	165	136	21.3	177	Essential hypertension; cystocele; cardiac asthma
55	45	F	170	136	25.0	280	Essential hypertension; chronic myocarditis
56	56	F	192	150	28.0	326	Essential hypertension; varicose veins
57	51	F	190	148	28.4	213	Essential hypertension; infestation by worms (T. saginata)
58	58	F	184	142	29.6	192	Essential hypertension; myofibrositis
59	37	F	187	144	29.9	229	Essential hypertension; diabetic type of dextrose tolerance curve
60	45	F	182	139	30.9	247	Essential hypertension; diabetic type of dextrose tolerance curve; coronary sclerosis; chronic myocarditis
61	46	F	179	136	31.6	278	Diabetes mellitus; coronary sclerosis; sinusitis
62	41	F	194	144	34.7	217	Essential hypertension; cystocele; rectocele
63	43	F	177	131	35.1	296	Diabetic type of dextrose tolerance curve; chronic cystitis
64	40	F	168	124	35.5	260	Diabetic type of dextrose tolerance curve
65	34	F	164	120	36.7	205	Diabetic type of dextrose tolerance curve; syphilis; chronic bronchitis
66	42	F	168	122	37.7	348	Diabetes mellitus
67	48	F	194	140	38.6	221	Essential hypertension
68	55	F	214	151	41.6	210	Diabetes mellitus; cervical polyp
69	32	F	178	125	42.4	245	Diabetic type of dextrose tolerance curve; endocervicitis
70	53	F	202	141	43.2	212	Diabetes mellitus; interdigital blastomycosis
71	35	F	188	128	46.7	278	Essential hypertension
72	39	M	238	145	64.1	153	Essential hypertension
73	50	F	233	142	64.1	270	Diabetic type of dextrose tolerance curve
74	42	F	225	136	65.4	229	Diabetic type of dextrose tolerance curve
75	50	F	241	143	68.5	254	Arteriosclerosis; cystocele
76	48	F	225	132	70.5	178	Essential hypertension; myocardial insufficiency; chronic endocervicitis
77	42	F	208	134	122.3	181	Essential hypertension; menorrhagia
78	42	F	330	145	128.0	279	Diabetic type of dextrose tolerance curve; varicose veins
Average						238 ± 46 mg. of cholesterol per 100 cc. plasma	

markedly obese patients (cases 39, 41 to 45, 47 to 50, 52 and 53). The mean cholesterol for the group was 194 ± 43 mg.

Table 3 gives the results obtained in twenty-five subjects in whom essential hypertension, diabetes mellitus or arteriosclerosis was associated with (or resulted from) the obesity. In this group are included

all cases in which the patients showed a diminished tolerance to ingested carbohydrate as determined by the dextrose tolerance test (these are the prediabetic patients).

In thirteen cases of obesity complicated by essential hypertension, three patients showed a definitely elevated plasma cholesterol (cases 55, 56 and 71); in four cases associated with diabetes mellitus, two patients had hypercholesteremia (cases 61 and 66); in seven prediabetic patients, four showed an elevated cholesterol (cases 63, 64, 73 and 78); in one case of obesity associated with arteriosclerosis there was moderate hypercholesteremia (case 75). In the remaining cases, the plasma cholesterol either was only moderately elevated (according to our standards of

TABLE 4.—*Cholesterol Content of the Plasma in Eleven Cases of Obesity Complicated by Arthritis*

Case	Age	Sex	Weight, Lbs.	Ideal Weight, Lbs.	Overweight, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Associated Clinical Conditions
79	60	F	164	135	20.0	180	Osteo-arthritis; mild endocervicitis
80	47	F	175	143	22.4	274	Osteo-arthritis; cystocele; rectocele
81	34	F	144	114	26.3	170	Gonococcal arthritis; pruritus vulvae; mild endocervicitis
82	46	F	183	143	27.9	178	Osteo-arthritis
83	45	F	173	132	31.1	274	Osteo-arthritis; pruritus vulvae
84	50	F	197	144	36.8	168	Rheumatoid arthritis; cystocele; endocervicitis; parametritis
85	57	F	187	134	39.6	229	Rheumatoid arthritis
86	28	F	186	130	43.0	222	Rheumatoid arthritis; chronic endocarditis; mitral regurgitation
87	34	F	187	130	43.9	227	Osteo-arthritis
88	55	F	218	143	52.5	441	Osteo-arthritis
89	50	F	220	144	52.7	305	Osteo-arthritis; varicose veins
Average.....						243 ± 77 mg. of cholesterol per 100 cc. plasma	

normality) or indicated a high normal; rarely was hypocholesteremia observed. The mean cholesterol for this group was 238 ± 46 mg.

It should be mentioned here that dextrose tolerance tests were not carried out in all of the ninety-four cases reported. In view of the results obtained in the prediabetic patients, it seems fair to postulate that of the six cases in the uncomplicated group showing hypercholesteremia, some might have shown a diminished tolerance for carbohydrate had the test been carried out and would therefore correctly belong in the former group.

Table 4 indicates the results obtained in eleven cases of obesity associated with either rheumatoid or gonococcal arthritis, or with osteoarthritis. It is interesting to note that only the moderately obese suffer from arthritis; the percentage of overweight in the eleven cases ranged from 20 to 53.

The plasma cholesterol showed marked differences in individual cases; in case 84 the cholesterol was 168 mg. and in case 88, 441 mg.

Because of these wide variations, it was considered advisable to place the two subjects in a separate group. The probable significance of these results will be considered later. The mean cholesterol for the group was 243 ± 77 mg. The high standard deviation is indicative of the wide variations encountered.

Table 5 shows the results obtained in five cases of obesity complicated (or caused) by endocrine disturbances.

The three obese subjects with hypo-ovarian dysfunction had a normal plasma cholesterol (cases 90, 92 and 94); in one case associated with hypothyroidism, hypercholesteremia was present (case 91); in another with acromegaly there was also a distinctly elevated plasma cholesterol (case 93). The mean cholesterol for the group was 224 ± 47 mg.

TABLE 5.—*Cholesterol Content of the Plasma in Five Cases of Obesity Complicated by Endocrine Diseases*

Case	Age	Sex	Weight, Lbs.	Ideal Weight, Lbs.	Over-weight, per Cent	Plasma Choles-terol, Mg. per 100 Cc.	Associated Clinical Conditions
90	26	F	190	122	55.7	218	Hypo-ovarian dysfunction; amenorrhea
91	30	F	205	124	65.3	264	Hypothyroidism
92	27	F	227	137	65.7	161	Hypo-ovarian dysfunction
93	42	F	280	169	65.7	289	Acromegaly
94	32	F	222	128	73.4	186	Hypo-ovarian dysfunction
Average.....						224 ± 47 mg. of cholesterol per 100 cc. plasma	

COMMENT

A detailed discussion of the causal relationship between obesity, on the one hand, and essential hypertension, diabetes mellitus and arteriosclerosis, on the other, is beyond the scope of this paper. Suffice it to say that clinicians have stressed such a relationship for many years; health institutes and life insurance companies have published pertinent statistics which apparently prove that these degenerative diseases occur with great frequency in persons who are overweight.

We are impressed by the fact that degenerative diseases, in contrast to the purely inflammatory or productive types, are usually associated with an increased blood cholesterol. Cell degeneration rather than cell destruction is accompanied by hypercholesteremia, e. g., in nephrosis, arteriosclerosis and similar conditions. The cellular disintegration that occurs in inflammatory processes and in the cachexias resulting from a variety of morbid lesions is generally associated with a moderate to a marked diminution of the cholesterol content of the blood.

Our results have shown that in obese subjects in whom obvious degenerative processes were lacking, the cholesterol content of the

plasma was within normal limits. When essential hypertension, diabetes mellitus or arteriosclerosis supervened, the blood cholesterol increased in many instances; it seems correct to conclude, therefore, that this hypercholesteremia represents the effect rather than the cause of the onset of the degenerative changes in obese subjects.

In a recent critical review on the subject of diet and blood lipoids, Bloor [27] stated that the continuous feeding of diets high in fat, on the one hand, and low in fat, on the other hand, produced definite changes in the level of the plasma cholesterol of dogs and rabbits. The cholesterol was always higher with a diet high in fats than with one low in fats; the difference was not so great in the dog, but it was marked in the rabbit. The fifty-three cases of uncomplicated obesity discussed in the preceding paragraphs may be considered as a representative group in which the obese state was probably due to the increased consumption of fat and of carbohydrate over a period of years. The cholesterol content of the plasma in these subjects, however, was usually within normal limits; in many instances the cholesterol was below the accepted standard for normality. Apparently, the continuous consumption of a diet high in fats over a period of months or years was even less effective in augmenting the blood cholesterol in human beings than in dogs.

A number of investigators have recorded the increased blood cholesterol in patients with diabetes mellitus (Joslin, Bloor and Gray,[28] Myers,[29] Malerba,[30] Labbé and Heitz,[3] Gray,[10] Rabinowitch,[22] White and Hunt [8] and others). In 1929 and 1933, Rabinowitch [22] stressed the prognostic significance of cholesterol determinations in diabetic patients. In eleven of our subjects in whom the obesity was complicated by diabetes mellitus or in whom a diminished tolerance for carbohydrate was evident from the dextrose tolerance test, six showed hypercholesteremia; the remaining five gave normal values.

Pribram and Klein,[31] Westphal,[32] and Waldorp [6] reported an augmented blood cholesterol in patients with essential hypertension. Weil,

27. Bloor, W. R.: Diet and the Blood Lipoids, J. Biol. Chem. **95**:663, 1932.

28. Joslin, E. P.; Bloor, W. R., and Gray, H.: The Blood Lipoids in Diabetics, J. A. M. A. **69**:375 (Aug. 4) 1917.

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30. Malerba, G. L.: Il tasso colesterinico del siero di sangue in varie forme morbose, Riforma med. **37**:602, 1921.

31. Pribram, H., and Klein, O.: Ueber den Cholesteringehalt des Blutserum bei arteriosklerotischem Hochdruck, Med. Klin. **20**:572, 1924.

32. Westphal, K.: Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes: IV. Cholesterin als tonogene Substanz der genuinen Hypertension im Zusammenspiel mit anderen Entstehungsbedingungen. Ztschr. f. klin. Med. **101**:584, 1925.

Guillaumin and Abricosoff [4] believed that there was a direct relationship between the height of the arterial tension and the degree of hypercholesteremia. In thirteen of our patients in whom the obese state was associated with hypertension, only three showed hypercholesteremia; the remaining ten gave high normal values, but the cholesterol was rarely low. The incidence of an increased blood cholesterol in hypertensive subjects found in our group of thirteen cases (23 per cent) was distinctly lower than that given by Westphal [32] (71 per cent). The maximum normal cholesterol adopted by us (250 mg.) is comparatively high according to the standards used by other investigators; this probably accounts for the difference in the incidence in the two series.

The blood cholesterol is reputed to be elevated in arteriosclerosis (Myers [29]). This hypercholesteremia forms the basis of Aschoff's [33] theory of the pathogenesis of arteriosclerosis. In one case of obesity complicated by arteriosclerosis studied in this series there was a moderately increased plasma cholesterol.

Gorham and Myers [21] studied five cases of arthritis and found the cholesterol content of the blood to be within normal limits. Pemberton and Robertson [34] reported fourteen cases and found the cholesterol to be subnormal; they felt that their findings supported the infectious theory of arthritis. In our eleven cases, the plasma cholesterol varied considerably in individual subjects; in general it may be stated (though this is by no means true for all of the cases) that the subjects with osteo-arthritis showed a higher blood cholesterol than those with infectious (rheumatoid or gonococcal) arthritis. Our series, however, is too small to permit us to make definite statements. The theoretical considerations outlined at the beginning of this discussion are apparently further supported by the findings in this group; the chronic arthropathy designated as osteo-arthritis (hypertrophic arthritis) is primarily a degenerative disease [35] and is more often associated, though not invariably, with a higher blood cholesterol than is the purely infectious or inflammatory type (rheumatoid or gonococcal arthritis). This phase of the subject deserves further investigation, the results of which should prove interesting.

Muller [36] recently reviewed the literature on the relation between the organs of internal secretion and cholesterol metabolism. The

33. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, pp. 142 and 143.

34. Pemberton, R., and Robertson, J. W.: Studies on Arthritis in the Army Based on 400 Cases: I. Preamble and Statistical Analysis, Arch. Int. Med. **25**: 231 (March) 1920.

35. Cecil, R. L.: A Text-Book of Medicine, Philadelphia, W. B. Saunders Company, 1930, p. 1254.

36. Muller, G. L.: The Cholesterol Metabolism in Health and in Anemia, Medicine **9**:119, 1930.

increased cholesterol content of the blood in hypothyroidism has been observed frequently both clinically and experimentally. A single case of obesity associated with hypothyroidism studied in this series showed a moderately elevated plasma cholesterol. In our three cases of obesity complicated by hypo-ovarianism there were normal cholesterol values; Blix,[14] however, was of the opinion that hypo-ovarian dysfunction was accompanied by hyperlipoidemia. In one case of acromegaly in this group there was hypercholesteremia; in the case reported by Gorham and Myers [21] the blood cholesterol was within normal limits.

SUMMARY

The plasma cholesterol in fifty-three obese subjects, in whom evidence of metabolic, arthritic or endocrine disturbances was lacking, was usually within normal limits.

The advent of diabetes mellitus, essential hypertension or arteriosclerosis in eighteen obese persons was associated in many instances with an augmented cholesterol content of the plasma. Four of seven overweight subjects who demonstrated a diminished tolerance to ingested carbohydrate as determined by the dextrose tolerance test, even though signs and symptoms of diabetes mellitus were lacking, showed an increased plasma cholesterol.

In four obese persons with infectious (rheumatoid or gonococcal) arthritis, the plasma cholesterol was usually within the normal limits; in seven cases with degenerative hypertrophic arthritis or osteo-arthritis, the cholesterol was often significantly elevated.

CONCLUSIONS

A high caloric diet, presumably high in carbohydrates and fats, which results in obesity is not accompanied by a rise of the plasma cholesterol in human beings.

The development of degenerative diseases (hypertension, diabetes, arthritis and arteriosclerosis) in the obese is as a rule followed, and not preceded, by hypercholesteremia. Therefore, the elevated concentration of the cholesterol in the blood in these degenerative conditions is usually to be regarded as a complication and not in the light of an etiologic factor.

MUSCULAR DYSTROPHY AND ATROPHY

CLINICAL AND BIOCHEMICAL RESULTS FOLLOWING THE ORAL ADMINISTRATION OF AMINO-ACIDS

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One of the most perplexing, and yet one of the most interesting problems encountered in medical practice in general, and in clinical neurology in particular, is constituted by that group of patients who are suffering from some form of muscular atrophy or dystrophy.

Perhaps the first complete descriptions of the various forms of muscular dystrophy and atrophy were presented about the middle of the nineteenth century during the time of Charcot [1] and his colleagues. Since that time numerous investigators have studied the problem in its various phases, and much information has been added toward a thorough comprehension of the characteristic clinical syndromes, with their associated pathologic lesions. Various theories as to the etiology of the condition have been presented and many therapeutic measures have been proposed, none of which have withstood the test of time.

The results of many studies have shown that in cases of muscular dystrophy the creatine metabolism of the muscles becomes deranged. In 1909, Levene and Kristeller [2] showed that the feeding of protein resulted in increased excretion of creatine in cases of muscular dystrophy. This observation was later confirmed by several investigators, chiefly Gibson and Martin [3] and Buell.[4] However, progress in this field was retarded

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A preliminary report of these studies was made at the meeting of the American Society of Biological Chemists held at Cincinnati in April, 1933.

1. Charcot, J. M.: Lectures on Diseases of the Nervous System, Paris, 1868; English translation, London, New Sydenham Society, 1877.

2. Levene, P. A., and Kristeller, L.: Factors Regulating the Creatinin Output in Man, Am. J. Physiol. **24**:45, 1909.

3. Gibson, R. B., and Martin, F. T.: Creatine Formation in a Case of Progressive Pseudohypertrophic Muscular Dystrophy, J. Biol. Chem. **49**:319, 1921.

4. Gibson, R. B.; Martin, F. T., and Buell, M. V. R.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, Arch. Int. Med. **29**:82 (Jan.) 1922.

for many years, because of the general belief that creatine in the muscles was a product of endogenous metabolism and that it could not be increased by the feeding of proteins or amino-acids. It seemed useless, therefore, to try to increase the formation of creatine by means of diet alone.

A recent review of the literature,[5] however, shows that there is evidence of the formation of creatine from such amino-acids as cystine, arginine and histidine. Brand, Harris, Sandberg and Ringer [6] were the first to show that the feeding of glycine caused an increase of 40 per cent in the excretion of creatine. Since there are about twenty amino-acids in the protein molecule, it is unlikely that one particular amino-acid could form creatine; it would seem, rather, that this might be a property of any one or all of them, as was definitely shown in the extensive studies of Barnes and one of us (H. H. B.[5]) in 1931. Proteins and amino-acids, when fed in sufficient amounts daily, increased the creatine content of muscles in young rats, and the excretion of creatinine in adult rats and human subjects.

It is well known from the work of many investigators that the patient who is suffering from muscular dystrophy is unable to retain creatine in his muscles. If this substance is ingested, most of it is excreted in the urine, making the patient practically "diabetic" as regards creatine. Recent work, which will be discussed later, has proved that the patient can form large amounts of creatine when certain amino-acids are fed in sufficient quantities. For a few weeks after such feeding there is an increased creatinuria, which gradually subsides, the creatine being retained in the muscles. At this time, clinical improvement and an increase in muscular function are noted.

It is also well known that a close relationship exists between creatine and carbohydrate metabolism. For instance, the creatinuria of starvation can be abolished by feeding carbohydrates. In 1925, Moren [7] and others noted a distinct, although not marked, clinical improvement in patients with muscular dystrophy to whom glycogen or sugar had been fed.

The first definite therapeutic effects of feeding glycine to patients suffering from muscular dystrophies were reported in 1932 by Milhorat, Techner and Thomas [8] in Germany.

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5. Beard, H. H., and Barnes, B. O.: The Influence of Feeding Proteins, Amino Acids and Related Substances upon Creatine-Creatinine Metabolism, J. Biol. Chem. **94**:49, 1931.

6. Brand, E.; Harris, M. M.; Sandberg, M., and Ringer, A. I.: Studies on the Origin of Creatine, Proc. Internat. Physiol. Congress, 1929, p. 36.

7. Moren, J. J.: Treatment of Muscular Dystrophies, Kentucky M. J. **23**:528, 1925.

8. Milhorat, A. T.; Techner, F., and Thomas, K.: Significance of Creatine in Progressive Muscular Dystrophy, and Treatment of This Disease with Glycine, Proc. Soc. Exper. Biol. & Med. **29**:609, 1932.

The following excerpt from their paper is of interest:

After a period of some weeks (depending upon how advanced the case is) the creatinuria begins to decrease, despite the continuance of glycine, until it falls to the former control level. While these changes in metabolism are taking place the patient improves in a remarkable manner. The first symptom manifested in half our patients was a curious feeling in the muscles which they describe as a "crawling, rumbling" sensation, which in one case was so severe that sleep was definitely interfered with. The next change in the clinical course is the disappearance of the fatigue that frequently constitutes a prominent and distressing symptom in this disease. The muscles that had previously felt tired and heavy now feel refreshed and lighter, and the patients often desire to make muscular movements they have not been able to make for a long time. Gradually, the function of certain muscle groups so improves that activities can be performed that had been impossible for years (climbing stairs, arising from the floor unaided, riding a bicycle). The degree of improvement differs not only in different patients, but in different muscles in the same patient. The time required for such improvement varies widely. One patient showed a remarkable improvement in three weeks; in another no definite increase in muscle function could be demonstrated at the end of nine weeks, although there was much subjective improvement.

These interesting results have stimulated several clinicians to use glycine, with and without ephedrine, in the treatment of muscular dystrophy and myasthenia gravis. In September, 1932, Boothby [9] of the Mayo Clinic, reported considerable success with glycine therapy in three cases of myasthenia gravis. In December of the same year, Boothby [10] reported six additional cases, making a total of nine of his own cases of myasthenia gravis in which this treatment was employed. Remen [11] reported remarkable improvement from glycine therapy in one case of myasthenia gravis. Schmitt,[12] Van Dalsem [12] and Trubek [12] also reported success in the treatment of myasthenia gravis with glycine or a combination of glycine and ephedrine. Reese [13] reported success with glycine in two cases of muscular dystrophy, the type of which was not stated, and in three cases of myasthenia gravis. Taylor [14] used gelatin, which contains about 25 per cent of glycine, in a case of myasthenia gravis with no effect, whereas when gelatin was administered in combination with ephedrine a remarkable clinical improvement was noticeable.

9. Boothby, W. M.: Myasthenia Gravis: A Preliminary Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:557 (Sept. 28) 1932.

10. Boothby, W. M.: Myasthenia Gravis: Second Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:737 (Dec. 28) 1932.

11. Remen, L.: Zur Pathogenese und Therapie der Myasthenia gravis pseudoparalytica, Deutsche Ztschr. f. Nervenh. **128**:66, 1932; cited by Boothby.[10]

12. Cited by Boothby.[10]

13. Reese, H. H.: Personal communication to one of us (H. H. B.).

14. Taylor, R.: A New Treatment for Myasthenia Gravis, South. Med. & Surg. **94**:790, 1932.

Milhorat [15] recently reported distinct clinical improvement in fourteen cases of progressive muscular dystrophy treated with glycine.[16] He found that this substance caused a decided increase in creatinuria, which was further enhanced by the addition of phosphates to the diet. Milhorat has shown histologically that after amino-acid therapy the muscles either show complete atrophy or present the picture of normal muscle fibers. He also proposed the older theory of abiotrophy, a hereditary disturbance manifesting itself by a loss of potentiality of the motor system, so that the stress of advancing years cannot be withstood. Our histologic studies have confirmed these observations. It appears that those muscle fibers in which the nuclei have begun to show pyknosis do not return to normal after amino-acid therapy is begun, but progress to complete atrophy with resultant fibrosis. However, those muscles in which the fibers have not reached this stage of degeneration present a normal histologic picture after therapy has been continued for a sufficient length of time.

Recently, we [17] presented a biochemical study of creatine-creatinine metabolism in various muscular conditions, namely, progressive muscular dystrophy, progressive spinomuscular atrophy, myasthenia from disuse and amyotrophic lateral sclerosis, wherein we especially noted that the creatinuria was greater in the cases of muscular dystrophy than in those cases in which atrophy was associated with lesions of the spinal cord. At the same time, Chanutin, Butt and Royster [18] reported five cases of pseudohypertrophic muscular dystrophy in one family. One boy was treated with glycine with remarkable results. Two brothers who were treated with creatine showed improvement for one month, and then became progressively worse.

Brand and Harris [19] are the only investigators who have so far reported unsatisfactory results from amino-acid therapy in cases of muscular dystrophy. These workers kept their patients on a meat-free

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15. Milhorat, A. T.: Ueber die Behandlung der progressiven Muskeldystrophie und ähnlicher Muskelerkrankungen mit Glykokoll, Deutsche Arch. f. klin. Med. **174**:487, 1933.

16. It might be well to mention here a note made by Quick (J. A. M. A. **99**:57 [July 2] 1932) who, citing the work of Milhorat, Techner and Thomas, noted that glycine or glycocoll (amino-acetic acid) should not be confused with the photographic developer which is sold under the trade name of "glycin." This compound is p-hydroxyphenylamino-acetic acid and is distinctly poisonous.

17. Beard, H. H., and Tripoli, C. J.: The Effect of Feeding Amino Acids in Cases of Muscular Dystrophy, J. Biol. Chem. **100**:14, 1933.

18. Chanutin, A.; Butt, H. R., and Royster, L. T.: A Study of Progressive Pseudohypertrophic Muscular Dystrophy in Children After the Administration of Glycine and Creatine, J. Biol. Chem. **100**:26, 1933.

19. Brand, E., and Harris, M. M.: Further Studies on the Administration of Glycine in Muscular and Neuromuscular Diseases, J. Biol. Chem. **100**:20, 1933.

diet low in purine during glycine therapy. We believe this to be an error, since normal protein metabolism must be maintained so that the "excess" amino-acid will be available for creatine formation. Brand and Harris did not observe the "crawling rumbling" sensations which are noted in those patients who respond to this type of therapy. Another fact of importance is that the patients were unable to retain the newly formed creatine in the body, since they continued to excrete this substance for as long as nine months after treatment. The work of these authors, however, has not progressed far enough at this time for definite conclusions to be drawn.

Kostakow and Slauck [20] recently reported beneficial results in seven patients with progressive muscular dystrophy treated with glycine, and added a note on its effect in spinal paralysis in children.

Table 1 presents a summary of the cases in which amino-acids are being used at the present time.

We wish to report in this paper our observations in cases of progressive spinomuscular atrophy, progressive muscular dystrophy, psychopathic inferiority complex with loss of muscle tissue from disuse, pseudohypertrophic muscular dystrophy and amyotrophic lateral sclerosis, in all of which amino-acid therapy was used. Our reasons for using glutamic acid in place of glycine in several cases are as follows: (*a*) According to Needham,[21] glutamic acid constitutes 16 per cent of the protein in the muscles. (*b*) We observed in earlier work that glutamic acid is a slightly better creatine former in young rats than glycine. (*c*) Glycine costs 2.6 cents a gram, while pure glutamic acid can be purchased for 1.2 cents a gram. (*d*) Glutamic acid is nontoxic, while glycine may be slightly toxic, as was noted when large doses were given to rats.[22]

The patients gave excellent cooperation, three of them collecting their own specimens of urine. The creatine-creatinine excretion was studied during a control period of from four to seven days before the administration of the amino-acids was begun. The total nitrogen, total creatinine and total creatine were determined daily in the twenty-four hour

20. Kostakow, S., and Slauck, A.: Glycine Treatment of Progressive Muscular Dystrophy, Deutsche med. Wchnschr. **59**:169 (Feb. 3) 1933.

21. Needham, D.: The Biochemistry of Muscle, London, Methuen & Co., 1932, p. 96.

22. Sullivan, M. X.; Hess, W. C., and Sebrell, W. H.: Studies on the Biochemistry of Sulphur: XII. Preliminary Studies on the Amino-Acid Toxicity and Amino-Acid Balance, Pub. Health Rep. **47**:75 (Jan. 8) 1932. Lillie, R. D.: Histopathologic Changes Produced in Rats by the Addition to the Diet of Various Amino Acids (Glycine, Lysine, Tryptophane, Cystine, Tyrosine and Glutamic Acid, and Glutathione, and of Mixtures of Some of Them), ibid. **47**:83 (Jan. 8) 1932.

TABLE 1.—*Summary of Cases in Which Amino-Acids Were Used*

Type of Disease	No. of Cases	Author	Therapy	Increase in Creatinuria	Clinical Results
Progressive muscular dystrophy	3	Milhorat, Techner and Thomas [8]	Glycine	++	Marked improvement
Pseudohypertrophic muscular dystrophy	3	Milhorat, Techner and Thomas [8]	Glycine	++	Marked improvement
Amyotrophic lateral sclerosis	1	Milhorat, Techner and Thomas [8]	Glycine	+	No improvement
Myasthenia gravis	9	Boothby [9]	Glycine with and without ephedrine	++	Marked improvement
Muscular dystrophy	2	Boothby [9]	Glycine	++	Slight improvement
Myasthenia gravis	1	Remen [11]	Glycine	....	Marked improvement
Myasthenia gravis	1	Schmitt [12]	Glycine and ephedrine	....	Marked improvement
Myasthenia gravis	1	Van Dalsem [12]	Glycine and ephedrine	....	Marked improvement
Myasthenia gravis	1	Trubek [12]	Glycine	....	Marked improvement
Muscular dystrophy	2	Reese [13]	Glycine	....	Good
Myasthenia gravis	3	Reese [13]	Glycine	....	Good
Myasthenia gravis	1	Taylor [14]	Gelatin with ephedrine	....	Marked improvement
Spinomuscular atrophy	1	Beard and Tripoli [17]	Glycine	+++	Slight improvement
Progressive muscular dystrophy	1	Beard and Tripoli [17]	Glutamic acid	++	Marked improvement
Amyotrophic lateral sclerosis	1	Beard and Tripoli [17]	Glutamic acid	....	No improvement
Amyotrophic lateral sclerosis	1	Beard and Tripoli [17]	Glutamic acid	++	Improvement for one month, then progressively worse
Psychopathic inferiority complex	1	Beard and Tripoli [17]	Glutamic acid	+	Improvement marked, possibly due partly to physiotherapy
Pseudohypertrophic muscular dystrophy	1	Beard and Tripoli [17]	Glutamic acid and glycine	..	Slight improvement after 2½ months
Progressive pseudohypotrophic muscular dystrophy	1	Chanutin, Butt and Royster [15]	Glycine	+ (?)	Marked improvement
Progressive pseudohypotrophic muscular dystrophy	2	Chanutin, Butt and Royster [15]	Creatine	..	Improvement for one month, then progressively worse
Progressive muscular dystrophy	9	Brand and Harris [19]	Glycine (meat-free, low purine diets)	++	No improvement
Progressive muscular dystrophy	14	Milhorat [18]	Glycine	++	First a rapid and then a slower improvement in the functional capacity of the muscles
Myotonia congenita	1	Milhorat [18]	Glycine	..	Good
Flaccid muscles	1	Milhorat [18]	Glycine	..	Good
Progressive muscular dystrophy	7	Kostakow and Slauck [20]	Glycine	++	Good

Total number of cases studied, 69.
Total number of cases clinically improved, 51.

specimen of urine in the case of each patient. At the beginning of the second period (shown by the arrows on the charts) 10 Gm. of glycine dissolved in milk was given to the patient suffering from progressive spinomuscular atrophy, and 10 Gm. of glutamic acid was given to the other five patients. The effect of the ingestion of amino-acid on the excretion of the total nitrogen, total creatinine, preformed creatinine and creatine in the first four cases is shown in figures 1, 4, 5 and 6.

Our studies were planned along several lines: first, to determine the creatine-creatinine metabolism of as many types of cases of muscular dystrophy and atrophy as possible, with particular attention to the effect of amino-acid therapy from both a biochemical and clinical aspect; second, to attempt a classification of the allied dystrophic-atrophic conditions on a pathologic-physiologic basis; third, to endeavor to formulate a basis for prognosis in the various types of cases.

REPORT OF CASES

The clinical data of our cases follow:

CASE 1.—A white man, aged 26, had been suffering from progressive spinomuscular atrophy for nine months. The early symptoms were muscular tremors, with weakness and fatigue on slight exertion, the muscles of the shoulder girdle and upper extremity being particularly affected. Marked asymmetrical body weakness was present, being more noticeable on the left than on the right side. Later, wasting of the interossei and lumbricales muscles of both hands was noted. Complete analyses of the blood and spinal fluid and roentgenologic examination gave negative results. Ten grams of glycine was given daily in milk beginning Dec. 1, 1932. After six weeks of this treatment the patient gained definitely in weight; there was a partial return of muscular strength, with a notable diminution of the tremulous twitchings in the left shoulder, but not in the right one. Since that time improvement has ceased.

CASE 2.—A white man, aged 36, had been suffering from progressive muscular dystrophy for twenty-one years. Atrophy began in the muscles of the shoulder girdle, gradually progressing throughout the muscular system of the thorax and abdomen until at the time the patient came under our observation the pelvic girdle was involved to such an extent that a "wobbling gait" resulted. Complete analyses of the blood and spinal fluid and roentgenographic examination gave negative results. All previous therapeutic regimens, including diet, physical therapy and stimulating tonic drugs, resulted in no definite effect on the progress of the disease. Ten grams of glutamic acid was given daily in milk, beginning Dec. 1, 1932. After one month of treatment, definite muscular improvement, both subjective and objective, was noted. There was an increase in weight; the "wobbling gait" disappeared, and the patient was able to walk four miles daily without fatigue. Improvement has been continuous in those muscles in which atrophic changes were taking place, but not in those in which resultant fibrotic changes of long standing had occurred. This finding is in keeping with the observations of Milhorat.[15]

Physical examination of the patient five months after the institution of glutamic acid therapy showed continued improvement. The strength of the muscles of the

back was marked. The left rectus abdominis muscle was markedly improved, whereas the right showed only slight improvement. The muscles of the arm and shoulder girdle, particularly those in which atrophic changes were practically complete, showed no evidence of improvement. However, those muscles which were not completely atrophic have regained their function and strength (figs. 2 and 3). The muscles of the leg, as noted, have continued to improve until little or no diminution from the normal in function or anatomy can be determined at the present time.

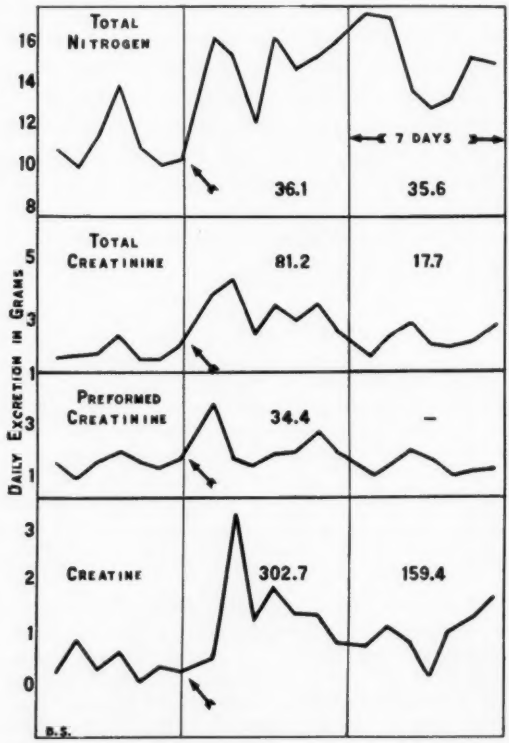

Fig. 1.—Effect of the ingestion of glycine on a patient with neuromuscular atrophy. The first seven days represent the control period. The arrows indicate the point at which 10 Gm. of glycine was given daily in milk to the patient. The figures in the succeeding periods show the average increase in per cent of the different constituents over that of the control period.

Case 3.—A white woman, aged 31, suffered from a psychopathic inferiority complex of five years' duration, following a disappointment in love. Physical examination revealed marked muscular atrophy of both lower extremities, resulting from a self-imposed, protracted stay in bed. The patient had been unable to walk for some time. Ten grams of glutamic acid was given in milk beginning on

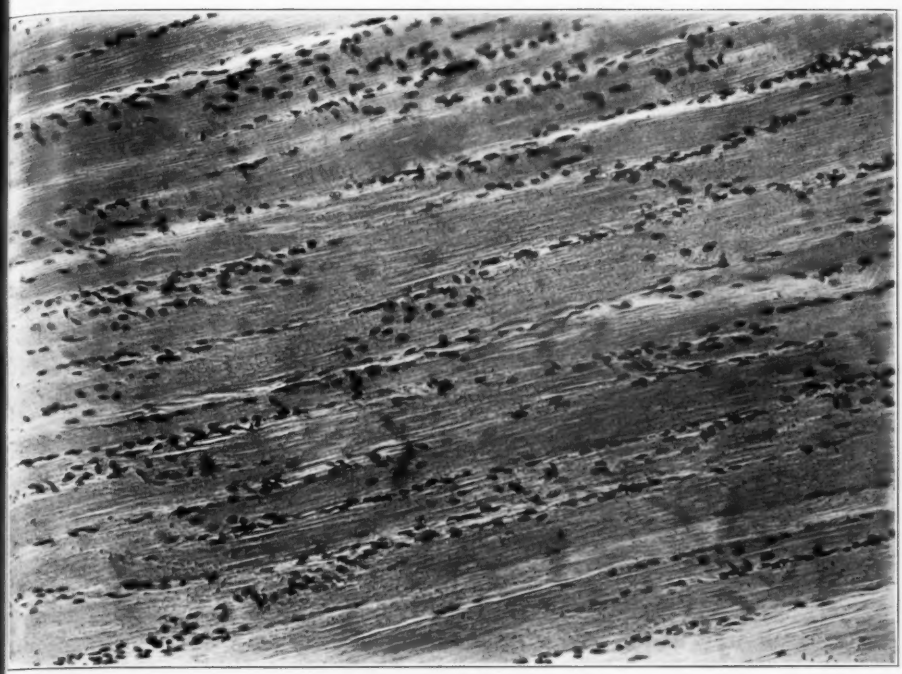

Fig. 2.—Photomicrograph of an excised muscle after amino-acid therapy. The tissue is normal. The specimen was taken from the gluteus maximus muscle of the patient in case 2; × 90.

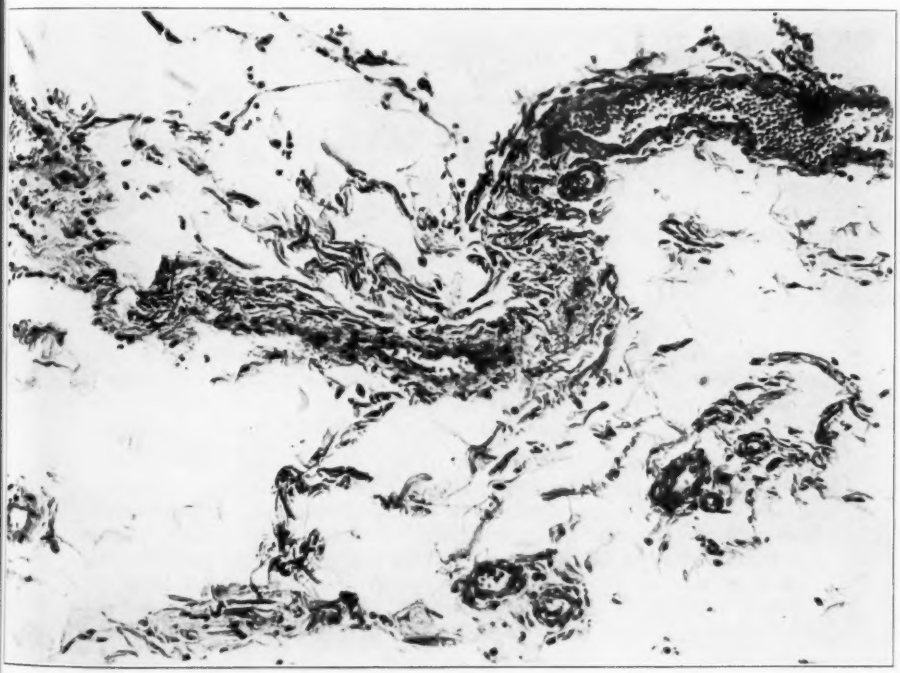

Fig. 3.—Photomicrograph of complete atrophic muscle tissue excised from a patient suffering from an advanced case of progressive muscular dystrophy, after amino-acid therapy. The return of muscular function is impossible. The specimen was taken from the trapezius muscle of the patient in case 2; × 90.

Dec. 13, 1932. General improvement, such as increase in body weight and strength and ability to walk, was noted after a few weeks of treatment. This improvement, however, may have been owing, in part at least, to the hygienic or physical therapy regimens which were simultaneously instituted.

Case 4.—A white man, aged 26, suffered from amyotrophic lateral sclerosis. In December, 1931, he noticed weakness and wasting in the arms, particularly in the left forearm and hand. The symptoms were progressive until December, 1932, at which time distinct weakness, atrophy and twitching of the muscles of the left shoulder, left side of the chest, arm, forearm and hand were noticeable, the latter

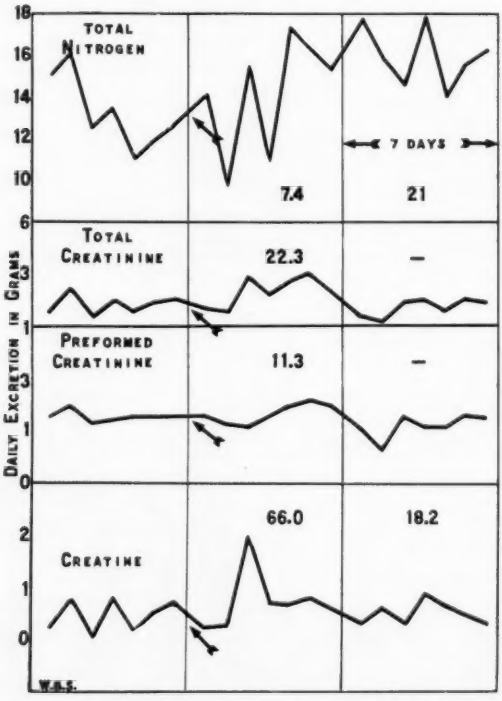

Fig. 4.—Effect of the ingestion of glutamic acid on a patient with progressive muscular dystrophy. The first seven days represent the control period. The arrows indicate the point at which 10 Gm. of glutamic acid was given daily in milk to the patient. The figures in the second and third weeks show the average increase in per cent of the different constituents over that of the control period.

progressing until marked atrophy of the interossei and lumbricales muscles was evident. This resulted in a very weak grip in the left hand. The patient was unable to flex the index finger, or facilitate "grouping" of the fingers of the left hand. Twitchings were marked in the left upper extremity and slight in the right upper extremity. The leg showed marked weakness with dysfunction of the anterior tibial group of muscles to the extent that the patient's normal gait was frequently interrupted by stumbling. Slight atrophy of the muscles was also

present. Complete analyses of the blood and spinal fluid and roentgenographic examination gave negative results. After 10 Gm. of glutamic acid in milk had been administered daily for four weeks, the left leg became stronger, and the patient no longer stumbled when walking. The muscle tone of the left arm improved to such an extent that the ability to flex and extend the left forefinger returned. Grouping was also improved in the left hand, but the muscular twitchings became more marked in the right arm. During the past few weeks the patient's progress seems to have ceased, and at the present time his clinical picture is stationary.

CASE 5.—A man, aged 45, was suffering from advanced pseudohypertrophic muscular dystrophy of twenty-three years' duration. The typical anterior curvature

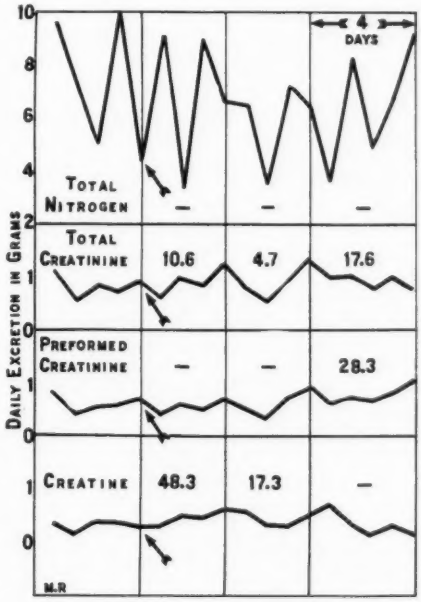

Fig. 5.—Effect of the ingestion of glutamic acid on a patient with a psychopathic inferiority complex. The first four days represent the control period. The arrows indicate the point at which 10 Gm. of glutamic acid was given daily in milk to the patient. The figures in the succeeding periods represent the average increase in per cent of the different constituents over that of the control period.

of the lower thoracic and lumbar segments of the spine with marked protuberance of the abdomen had taken place. The condition of the muscles was characteristic of the disease. The patient was unable to dress himself. He was so weak that he was able to assume a standing position only with the help of a support such as his desk, literally "climbing" up by using the muscles of his shoulder and arm. Of late he had begun to notice an increased difficulty in rising caused by weakness of these muscles. On Feb. 16, 1933, 10 Gm. of glutamic acid was administered, and this treatment was continued daily for one month without improvement. Later, glycine was substituted and the dosage increased to 20 Gm.,

administered twice daily. During a period of two and one-half months the patient began to show slight improvement, particularly a marked gain in body weight. Recently, ephedrine was added in an attempt to enhance the therapeutic effect of the amino-acid therapy. We believe that glycine therapy has checked the progress of the disease. Slight improvement, evidenced by a better hand grip and a more stable gait, has occurred, but the duration of therapy has not been sufficient to bring about greater return of function. We expect to see further improvement in this case.

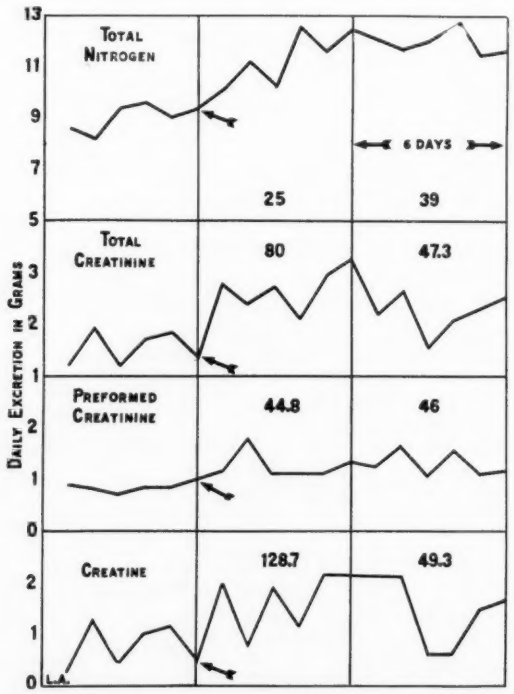

Fig. 6.—Effect of the ingestion of glutamic acid on amyotrophic lateral sclerosis. The first six days represent the control period. The arrows indicate the point at which 10 Gm. of glutamic acid was given daily in milk to the patient. The figures in the succeeding periods represent the average increase in per cent of the different constituents over that of the control period.

Case 6.—A white woman, aged 61, suffered from amyotrophic lateral sclerosis. She complained of pain in the back, weakness of the knees and dragging of the left foot. The family history was not important. Two years previous to examination the patient fell and has been very weak since that time. She has fallen several times during the past two years. Three weeks prior to examination her condition became steadily worse. She drags her left foot. Her knees are weak, and she is unable to walk alone. Her hands, especially the left, are weak and numb. The positive neurologic findings were: left foot drop; general increase of deep reflexes; positive Babinski and Hoffman sign bilaterally; muscular weakness exhibited in

the grip of the hand and extension of the foot; atrophy of the interossei muscles of the hands. Ten grams of glutamic acid has been administered daily since March 20, 1933. No clinical improvement has been noted up to the present time.

COMMENT

The results shown in figure 7 indicate that both creatine and creatinine may be formed from glycine or glutamic acid administered orally

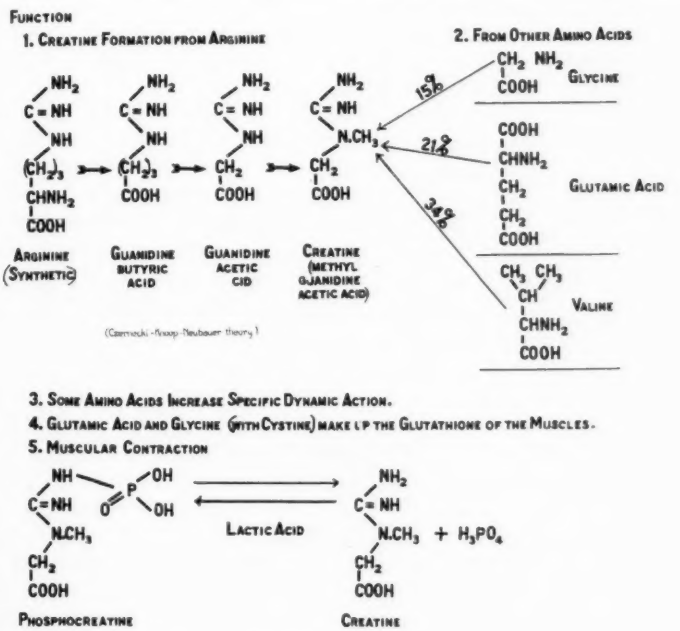

Fig. 7.—Graphic formulas showing the function of arginine and guanidine acetic acid and their conversion into creatine by methylation. The degree of methylation by various amino-acids is indicated by arrows in percentage values. Muscular contraction with its chemistry is graphically represented.

in large doses. These results are in accord with those of other investigators. In our previous study of young rats [5] in Cleveland it was observed that valine caused an increase of 34 per cent in muscular creatine, cystine, 37 per cent, glycine, 15 per cent, and alanine, 13 per cent. Guanidine acetic acid caused an increase of 48 per cent. Since arginine can be formed synthetically in the body, this may be a source of the guanidine grouping necessary for the formation of the

creatine.[23] We believe that the primary requisite for the formation of the creatine in the body is the methylation of this guanidine rest (possibly as guanidine acetic acid) to creatine. Since valine, with two methyl groups, and cystine, with two substituted methyl groups, produces more than twice as much creatine as glycine (the latter having only one substituted methyl group), it would seem that the degree of methylation per unit of time determines the degree of the formation of the creatine.

This may also explain the formation of creatine from choline and betaine, each of which contains three or more methyl groups. These substances, however, do not produce three times as much creatine as glycine, which may be owing to the fact that there is an upper limit to formation of the creatine from its precursors, in young rats, per unit of time. It is also well known that the body has the power to methylate certain compounds, and it is generally agreed that guanidine acetic acid, even though it does not occur normally in the body, nevertheless can be methylated to creatine when ingested. When this methylation process is increased by the ingestion of amino-acid increased formation of creatine and creatinine results. Therefore, creatine may be formed from ingested amino-acids, or its formation may be stimulated by these amino-acids. In view of the results obtained in our previous work and also in the treatment of patients described in this paper, we believe that creatine arises in the body from both exogenous and endogenous sources.

The formation of creatine is not the only function of the amino-acids. It is well known that glycine and glutamic acid increase the specific dynamic action of protein in the body. These two acids, with cystine, make up the glutathione of the muscles. Finally, each of these amino-acids is capable of forming sugar, and probably both assist in the construction of new proteins in the muscles. These facts are shown by the simultaneous increase in body weight, strength and muscular efficiency in our patients.

A few remarks might be made here on the therapeutic effect of the ingestion of amino-acid on the metabolism of the diseased muscles. The results of our own work and that of many other investigators show that the patient who is suffering from certain types of myopathies cannot

23. This view is in harmony with the well known Czernecki-Knoop-Neubauer theory of the origin of creatine from arginine (Czernecki, W.: Zur Kenntnis des Kreatins und Kreatinins im Organismus, Ztschr. f. phys. Chem. **44**:294, 1905. Knoop, F.: Ueber den physiologischen Abbau der Säuren und die Synthese einer Aminosäure im Tierkörper, ibid. **67**:489, 1910. Neubauer, O.: Abbau der Aminosäuren im Organismus, in Abderhalden: Biochemisches Handlexikon, Berlin, Julius Springer, 1911, vol. 4, p. 360. Hunter, A.: Creatine and Creatinine, London, Longmans, Green & Co., 1928, p. 223).

"fix" or retain creatine in the muscles. This valuable substance is continually lost in the urine and is accompanied by a gradual loss of muscle tissue and function. If creatine be given as such, most of it passes through the body and is excreted in the urine. Hence, feeding creatine does not increase the creatine content of the muscles, and no clinical improvement in the patient's condition takes place.

On the other hand, the amino-acids form creatine which at first is lost in fairly large amounts. After a few weeks it is retained in the muscles, and at this time the patient begins to show clinical improvement. It would seem, therefore, that the amino-acids supply a deficiency in muscle metabolism. This creatine, retained as phosphocreatine, serves over and over again to supply the energy for muscle contraction, and the muscular efficiency of the patient increases at a remarkable rate. That the amino-acids play a definite part in muscle metabolism is supported by the fact that as long as they are fed to the patient, he improves, yet this improvement may cease as soon as the therapy is discontinued, and the patient may revert to his original condition. Possibly amino-acids should be given to these patients for the remainder of their lives. However, more experimental evidence is necessary to confirm this opinion.

It is well known that glycine and glutamic acid can be synthesized in the body, and that they are not necessary for growth in the young animal. Nevertheless, it would seem that they play an important part in the metabolism of patients suffering from various forms of muscular dystrophy. More surprising still is the fact that the ingestion of either glycine or glutamic acid is effective. From the results of our previous work, we believe that any amino-acid of the protein molecule may produce similar results. When it is recalled that a protein molecule may contain about twenty amino-acids, it will be seen that nature has provided enough raw material for both muscle structure and function. No doubt it is possible that in the patient with muscular dystrophy (*a*) not enough protein is ingested, (*b*) that which is taken is not utilized to any great extent, (*c*) it is not ingested in the proper form for utilization in muscle metabolism or (*d*) there may be some dysfunction of protein digestion which results in the patient's inability to utilize properly the ingested or formed amino-acids. The latter point is under investigation at the present time, and our results will be published later.

Brentano [24] presented evidence to show that creatinuria is always associated with a reduction of the glycogen in the muscle. The disappearance of creatinuria is associated with an increase of glycogen in the muscle. Our clinical results also confirmed the belief that a dis-

24. Brentano, C.: Untersuchungen über die Entstehung der Kreatinurie: II. Mitteilung: Die Beziehungen zwischen Kreatinurie und Muskelglykogen, Arch. f. exper. Path. u. Pharmakol. **155**:21, 1930.

appearance of creatinuria was followed by increase not only of glycogen in the muscles but also of protein. This was shown by the increase in body weight of our patients, after amino-acid therapy. This result has never occurred before while the patients were on their usual full dietary regimen.

It is also possible that the feeding of sugar may stimulate creatine metabolism, since it is generally believed that lactic acid furnishes the energy for the resynthesis of phosphocreatine from creatine and phosphoric acid. Moren [7] stated that research has shown that in cases of muscular dystrophy a disturbance of sugar metabolism takes place, caused possibly by a lowering of the amount of glycogen in the muscles. Eaton [25] and also Farnell [25] have noticed beneficial results from feeding sugar to patients suffering from muscular dystrophies.

TABLE 2.—*Classification of Syndromes of Muscular Atrophy and Dystrophy*

Group I. Primary Myopathies:	Group II. Progressive Nuclear Muscular Atrophy:
1. Primary muscular dystrophy (usually of the lower limbs):	1. Mainly of small muscles of the hand (Aran-Duchenne)
(a) Pseudohypertrophic (Duchenne)	2. Hereditary, familial, of infancy and childhood (Werdnig-Hoffmann)
(b) Facio-scapulo-humeral (Landouzy-Dejerine)	3. Subacute and chronic poliomyelitis
(c) Bulbar (Hoffmann)	4. Bulbofacial of childhood (Fazio-Londe)
(d) Juvenile scapular (Erb-Zimmerlin)	5. Progressive bulbar palsy (glosso-labio-laryngeal, of Bouchard)
(e) Infantile-hereditary (Leyden)	6. Chronic progressive ophthalmoplegia (von Graefe)
2. Myasthenia gravis	7. Amyotrophic lateral sclerosis (Dejerine)
3. Amyotonia congenita (Oppenheim)	8. Progressive spinal muscular atrophy
4. Myotonia congenita (Thomsen)	
(a) Early life (hereditary)	
(b) Myotonia acquisita	
5. Myotonia atrophica	

Greater clinical improvement results from amino-acid therapy in the conditions listed in group I than in those listed in group II.

Not only is the classification of the syndromes of muscular atrophy and dystrophy confusing, but not infrequently the names are used interchangeably. Certainly a pathologic-clinical classification is conducive to a much clearer comprehension of the disease processes than is an eponymic classification.

Therefore, we believe that the following classification based on Wechsler's text [26] is a satisfactory one (table 2).

It would seem that those conditions listed in group I would be more properly generally classified as dystrophies, and those in group II as atrophies. In other words, the atrophies result from nuclear lesions in the central nervous system, whereas the dystrophies are caused by primary lesions in the muscle which probably are primarily abiotrophic. A review of the cases presented reveals interesting results. Certainly in those cases which fall into the group termed dystrophies, with the excep-

25. Cited by Moren.[7]

26. Wechsler, I. S.: A Text-Book of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1931, p. 191.

tion of the cases of Brand and Harris [19] in which we believe a meat-free diet low in purine played a most important part in the unsuccessful results, clinical improvement has been uniform. Not only was the progress of the disease in all cases inhibited, but the clinical condition was improved, the improvement being graded as slight, good or marked. The most striking recovery was noted in the cases of myasthenia gravis, pseudohypertrophic muscular dystrophy and progressive muscular dystrophy. On the other hand, the cases which fall into group II seem to be little affected by the administration of the amino-acids. In these cases, the lesions occur primarily in the central nervous system and the atrophy is secondary to the changes in the spinal cord or to nuclear changes. In one of our cases a definite increase in creatinuria occurred with, however, only slight clinical improvement.

The variation in the clinical results in the two groups of cases is most impressive, and it is not unlikely that the clinical results following the administration of amino-acids in sufficient amounts will possibly be additional criteria in distinguishing some of the more vague syndromes so frequently seen, which often defy classification even by the most able neurologists.

In passing, we wish to make a note concerning the use of amino-acids in the diet in cases of poliomyelitis in the acute, convalescent and chronic stages, and also in postpoliomyelitic paralyses. By this therapy we may at least preserve the tone of the paralyzed muscles until regeneration of the affected nerves occurs, and thus prevent the grave atrophic changes that usually result from the lesions of the nerve. Our observations so far have been very encouraging in two cases, but our progress is somewhat slow owing to the small number of cases under observation at the present time. The results, whether positive or negative, will certainly be of interest and will be reported later.

SUMMARY

A review of the recent literature concerning the origin and function of creatine in the muscles, with particular reference to clinical results in patients suffering from various forms of muscular dystrophy and atrophy, is presented.

The clinical results obtained from the administration of glycine or glutamic acid, fed in 10 or 20 Gm. daily doses, in six of our own cases of various dystrophies and atrophies are recorded. The average increases in the excretion of creatine ranged from 48 to 303 per cent, and in the excretion of creatinine from 11 to 46 per cent.

The total number of cases reported by ourselves and others to date is 69, in 51 of which decided clinical improvement has been observed after amino-acid therapy. The most marked clinical improvement is

noted in those cases grouped as muscular dystrophies. Only slight clinical improvement, if any, was noted in cases grouped as progressive nuclear muscular atrophy.

Four possible etiologic factors which may play a part in the pathologic metabolism of the patient with muscular dystrophy are suggested.

It would appear that the administration of creatine is not an effective therapeutic measure.

A new theory of the origin of creatine in the body, based on this and previous work, is presented.

Drs. L. L. Cazenavette, M. S. Freiman, U. Giles, L. S. Hill and H. R. Unsworth permitted the use of their patients; Dr. William M. McCord assisted in the preparation of the amino-acids, and Dean Arthur Vidrine of the medical center gave financial aid which made these studies possible.

BACTERIOLOGIC STUDY OF THROATS IN RHEUMATIC AND NONRHEUMATIC FEVER

WITH SPECIAL REFERENCE TO HEMOLYTIC STREPTOCOCCI

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Clinicians have long recognized that an attack of acute rheumatic fever is preceded in many instances by sore throat or some other infection of the upper respiratory tract. This is true for both an initial attack of the disease and an exacerbation of symptoms. Williams,[1] in discussing this subject, concluded that "the majority of all cases of rheumatic fever are preceded by sore throat or some upper respiratory infection." Observers of this relationship have further noted that the rheumatic symptoms do not immediately follow the respiratory infection, but that there is an interval of from ten to twenty-one days. Recently a number of careful investigators called attention to the presence of hemolytic streptococci in the throats of persons who later manifest the symptoms of acute rheumatic fever. They laid great emphasis on this point, believing that an etiologic relationship exists. An equally careful group of observers, however, believe that such a conclusion at the present time is unwarranted. Some maintain that green-producing streptococci are the causative agents; others think that no single streptococcus, but rather an entire group, is responsible for the symptoms of the disease, and still others insist that an agent unrelated to the streptococci, as, for example, a filtrable virus, plays the important rôle.

The present study was undertaken with a view to gathering further data on the presence of hemolytic streptococci in the throats of patients with rheumatic fever and to attempt to correlate, if possible, their presence with the clinical symptoms of the disease. A large number of controls were included in the study. There were certain inherent

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From the Medical Division of Montefiore Hospital for Chronic Diseases, and the Department of Bacteriology, New York University and Bellevue Hospital Medical College.

1. Williams, A. W.: Streptococci in Relation to Man in Health and Disease, Baltimore, Williams & Wilkins Company, 1932.

difficulties in the problem which soon became apparent. One of them was pointed out by Andrews, Derick and Swift [2] in 1926. They called attention to the fact that a large number of patients with rheumatic fever who enter a hospital do so after they have completely recovered from infection of the throat. Of 122 patients with rheumatic fever who were admitted to the hospital of the Rockefeller Institute, only 5 had active infection of the throat at the time of admission. A second difficulty lies in the fact that the symptoms of the upper respiratory tract may be so mild as to be overlooked, and therefore no history of any such symptoms is obtained when the patient is admitted to the hospital. This is especially true in the case of young children. In addition, a bacteriologic examination of throats after the acute infection has subsided does not always reveal the causative organism. The flora of the throat, especially as regards pathogenic organisms, is by no means constant. Coburn and Pauli,[3] in their study of the throats of patients with rheumatic fever, observed that Streptococcus haemolyticus tended to become conspicuous during the quiescent phase of the disease and absent during an exacerbation of symptoms. In spite of these difficulties, a number of investigators have insisted that the time when an exacerbation of rheumatic symptoms would appear might be predicted with a fair degree of accuracy by ascertaining the presence of hemolytic streptococci in the throat.

REVIEW OF THE LITERATURE

In 1886, Haig-Brown,[4] the medical officer at a boys' school in England, observed that "an attack of acute rheumatism is very frequently preceded by one of acute tonsillitis." The interval might be five or six weeks, but usually it was ten days or a fortnight. The two diseases might even be coincident. He also noted that among 345 previously healthy boys with tonsillitis, heart disease developed in 21.

There is a wide difference of opinion among observers as to the effect of tonsillectomy in preventing attacks of acute rheumatic fever. In 1920, St. Lawrence [5] stated that "tonsillectomy would seem to be the most important measure at present available for the prevention of

2. Andrews, C. H.; Derick, C. L., and Swift, H. F.: A Study of Hemolytic Streptococci in Acute Rheumatic Fever, J. Exper. Med. **43**:13, 1926.

3. Coburn, A. F., and Pauli, R. H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process; Observations on Ecology of Hemolytic Streptococcus in Relation to Epidemiology of Rheumatic Fever, J. Exper. Med. **56**:609, 1932.

4. Haig-Brown, C.: Tonsillitis in Adolescents, London, Baillière, Tindall & Cox, 1886.

5. St. Lawrence, W.: Effect of Tonsillectomy on the Recurrence of Acute Rheumatic Fever and Chorea, J. A. M. A. **75**:1035 (Oct. 16) 1920.

acute rheumatic fever." Eighty children were observed during an average period of three and a half years following tonsillectomy. One or more attacks of acute rheumatic fever had occurred in 42 before the tonsils were removed. After tonsillectomy there was no recurrence in 35, or 84 per cent.

In the same year, Poynton, Paterson and Spence,[6] in England, found that removing the tonsils did not prevent the recurrence of the disease. They pointed out, however, that the throat is a common portal of entry for the rheumatic infection. They based this conclusion on a study of 172 rheumatic children. In 22 of the cases acute tonsillitis had immediately preceded the attack of rheumatism; in 38 there were large and unhealthy tonsils, and in 17 the tonsils had been removed.

Ingerman and Wilson[7] also studied the relationship between tonsillectomy and the occurrence of rheumatic manifestations. They found that 76 per cent of 88 cases of tonsillitis were followed by a recurrence of rheumatic manifestations within from one to eleven years after tonsillectomy. In a group of 97 patients on whom tonsillectomy had not been performed and who were studied over a similar period, 80 per cent showed a recurrence of rheumatic manifestations.

Kaiser[8] followed for a period of three years a group of 1,200 children who had had their tonsils removed and an equal number who had had no operation. He concluded that tonsillectomy had not influenced the incidence of chorea or rheumatism. A history of rheumatic symptoms had been obtained from 46 children previous to the operation. Three years later, 129 had similar disorders, and of this number 116 had their first attack of rheumatism after the operation. In the group not operated on, 128 had rheumatic symptoms.

Mackie[9] noticed that complete removal of the tonsils when evidence of infection was present, together with appropriate treatment of other foci of infection, seemed to reduce but did not wipe out recurrences of rheumatic fever. Of 80 patients whose tonsils had been enucleated after an attack of acute rheumatic fever, 34, or 42.5 per cent, had recurrences. This group had been observed for about three years. Of 207 patients on whom tonsillectomy had not been performed, 125, or 60.3 per cent, had recurrences. This group had been observed over four years.

6. Poynton, F. J.; Paterson, D., and Spence, J. C.: Acute Rheumatism in Children, Lancet **2**:1086, 1920.

7. Ingerman, E., and Wilson, M. G.: Rheumatism: Its Manifestations in Childhood Today, J. A. M. A. **82**:759 (March 8) 1924.

8. Kaiser, A. D.: Effect of Tonsillectomy on the General Health of 1,200 Children, as Compared with an Equal Number Not Operated On, J. A. M. A. **83**:33 (July 5) 1924.

9. Mackie, T. T.: Rheumatic Fever: An Analytical Study of 393 Cases of Rheumatic Fever and 89 Cases of Chorea, Am. J. M. Sc. **172**:199, 1926.

Boas and Schwartz,[10] in 1927, studied the records of 53 children under 15 years of age with rheumatic heart disease at Montefiore Hospital. Thirty-nine of these patients had febrile episodes. The authors found that 20 of these 39 patients and 10 of the remaining 14, who had been afebrile, had had their tonsils removed. In addition, only 10 of the 63 episodes of fever exhibited by the 39 patients were associated with tonsillitis. They concluded that the tonsil is not so important a portal of entry for rheumatic infection as has been generally supposed and that tonsillectomy appears to be of little avail in reducing the hazards of reinfection.

Irvine-Jones [11] made cultures from the throats of rheumatic children and found that hemolytic streptococci were usually present during convalescence and only rarely during the period of acute sore throat. The streptococci obtained from the upper respiratory tract of rheumatic children were identical with those from normal children.

McCulloch and Irvine-Jones [12] studied 150 children at the Children's Heart Clinic of Washington University over periods varying from nine months to eleven years. In this group attacks of rheumatic fever or chorea occurred 304 times. One hundred and ninety-seven of these attacks had apparently been precipitated by colds or sore throats. The authors believed that tonsillectomy, when followed by hygienic measures, is of value in decreasing the number of recurrences of rheumatic fever and chorea. In a group of 90 children with constant infection in the nasopharynx, the percentage of recurrences of rheumatic fever and chorea was paralleled by the success obtained in combating the infection and improving the living conditions of the patients.

Nabarro and MacDonald,[13] in 1929, made repeated cultures from the tonsils of 50 rheumatic and 48 nonrheumatic children. They found that the streptococci isolated from the tonsils of the subjects with rheumatism did not differ materially from those isolated from the tonsils of the subjects free from rheumatism. Even when the cultures were grown on Crowe's medium,[14] which is supposed to bring out the most minute differences in the appearance of the colony, these investigators

10. Boas, E. P., and Schwartz, S. P.: Some Modes of Infection in Rheumatic Fever, Am. Heart J. **2**:375, 1927.

11. Irvine-Jones, E. I. M.: Skin Sensitivity of Rheumatic Subjects to Streptococcus Filtrates and Its Relationship to Rheumatic Fever, Arch. Int. Med. **42**:784 (Nov.) 1928.

12. McCulloch, H., and Irvine-Jones, E. I. M.: The Rôle of Infection in Rheumatic Children, Am. J. Dis. Child. **37**:252 (Feb.) 1929.

13. Nabarro, D., and MacDonald, R. A.: Bacteriology of the Tonsils in Relation to Rheumatism in Children, Brit. M. J. **2**:758, 1929.

14. Crowe, H. W.: Differentiation and Classification of Non-Haemolytic Streptococci by Use of Crowe's Medium, Ann. Pickett-Thomson Research Lab. **3**:251, 1927.

were unable to differentiate the organisms obtained from the two sources. They therefore concluded that no specific streptococcus is the cause of rheumatism.

Glover [15] called attention to an epidemic of tonsillitis in the Royal Air Force at Halton, England, in 1928. Four hundred and twenty-seven patients were admitted to the hospital. There were 41 cases of acute rheumatism, in 17 of which there were symptoms of carditis. It was observed that the peak of the tonsillitis epidemic preceded by some two or three weeks the crest of the epidemic of acute rheumatism.

Schlesinger,[16] as a result of a four year clinical study of the relationship between infection of the throat and rheumatic relapses at the West Wickham Hospital for children with rheumatic heart disease, concluded that relapses are largely brought about by acute and often extremely mild infections of the throat. In a group of 62 rheumatic patients with tonsillitis, 40 showed no sequelae. The remaining 22, however, after an approximate interval of from ten to twenty-one days, showed a rise in temperature and a relapse of rheumatism. For several months previous to the attack of tonsillitis these patients had had quiescent valvular lesions and a normal temperature and pulse rate. The streptococci recovered from the tonsils were occasionally hemolytic, but for the most part they were of the viridans type that is commonly found in normal throats. Schlesinger therefore did not favor the theory that a specific streptococcus is the cause of rheumatism but was more inclined to the view that the whole group of these micro-organisms is in some way responsible. He observed that children who had had their tonsils removed were less prone to nasopharyngeal infections than those who retained them. However, tonsillectomy did not preclude acute infection of the throat, and when this did occur there seemed to be greater likelihood of a rheumatic relapse. Recurrences following acute nasopharyngeal infection were observed in 50 per cent of the children who had had the operation and in only 30 per cent of those who had not. The severity of the relapses in both groups was about the same.

Sheldon [17] reported a two year clinical study of children with rheumatism at the Cheyne Hospital for Children and the Lancing Convalescent Heart Home. He confirmed Schlesinger's observation that if a child has had a rheumatic infection a relapse is likely to follow an acute infection of the throat within, roughly, from ten to twenty-one days. He also found that removal of the tonsils did not influence the

15. Glover, J. A.: Milroy Lectures on Incidence of Rheumatic Diseases: Incidence of Acute Rheumatism, Lancet **1**:499, 1930.

16. Schlesinger, B.: The Relationship of Throat Infection to Acute Rheumatism in Childhood, Arch. Dis. Childhood **5**:411, 1930.

17. Sheldon, W.: On Acute Rheumatism Following Tonsillitis, Lancet **1**:1337 (June 20) 1931.

likelihood of a rheumatic relapse. He was not able to confirm the finding of Schlesinger that the continued administration of acetylsalicylic acid following tonsillitis would prevent any serious rheumatic relapse.

Collis [18] investigated the flora of the throat in the epidemic of tonsillitis that was described by Sheldon at the Cheyne Hospital for Children. He found that rheumatic relapses occurred in 9 of 11 children in whom hemolytic streptococcic sore throat had developed. In those who had an infection of the upper respiratory tract associated with some organism other than the hemolytic streptococcus there were no relapses.

Glover and Griffith [19] described two epidemics of acute rheumatism in the English public schools. In the first there were 136 cases of sore throat, 15 of which were followed by acute rheumatism (the proportion being slightly greater than 1 in 10). Tonsillar and pharyngeal cultures from 8 of these patients with rheumatism were examined. Five of them yielded hemolytic streptococci, all of the same serologic type. A year later there was another outbreak of tonsillitis. Hemolytic streptococci were found in 77 cases, the majority of which were of one serologic type, but this type was different from that found the previous year. In 6 of these cases rheumatic symptoms appeared.

Swift [20] observed that most patients, both children and adults, give a history of repeated nonspecific infections of the respiratory tract, including the tonsils, sinuses and middle ear, extending over several years, before a typical attack of rheumatic fever is ushered in by a severe focal infection.

Coburn [21] and Coburn and Pauli [3] reported the results of an extensive series of observations on the incidence of acute rheumatic fever. They believed that there is a close relationship between the presence of hemolytic streptococci in the throats of patients with this disease and the occurrence of rheumatic symptoms. They found that in tropical environments hemolytic streptococci are unusual in the flora of the throat and that rheumatic fever is rare. On the other hand, in New York City, where these organisms are frequently found, there are numerous cases of the disease. When the streptococcus becomes implanted in the throat there may be either no symptoms or, possibly, only those of a slight cold. In the majority of persons this local disease is the only manifestation of the invasion of the tissues. In a small

18. Collis, W. R. F.: Acute Rheumatism and Haemolytic Streptococci, Lancet **1**:1341 (June 20) 1931.

19. Glover, J. A., and Griffith, F.: Acute Tonsillitis and Some of Its Sequels, Brit. M. J. **2**:521, 1931.

20. Swift, H. F.: Factors Favoring the Onset and Continuation of Rheumatic Fever, Bull. New York Acad. Med. **7**:429, 1931.

21. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.

minority, however, this is followed by acute rheumatic fever. These investigators concluded from a study of ambulatory rheumatic patients over a period of four years that persons who escape respiratory disease remain free from rheumatic symptoms and that the majority of patients who contract hemolytic streptococcic pharyngitis have shortly afterward a definite recrudescence of rheumatism.

Bradley [22] reported two epidemics of acute rheumatism in an English school which had been free from such infection for about forty years. The epidemics were paralleled by waves of hemolytic streptococcic sore throat. Prior to these epidemics Streptococcus haemolyticus had rarely been detected.

Paul and Salinger [23] carefully studied the histories of 15 families in which the incidence of rheumatic fever was high. From their own evidence and from that obtained from other investigators they concluded that rheumatic fever is an infectious disease. Environmental factors probably play an important part, because flare-ups seem to sweep through a family in recurrent waves. These investigators thought that droplet infection attendant on disease of the upper respiratory tract may be responsible for the spread of the unknown virus. During the epidemic waves children between the ages of 4 and 12 seem to be particularly susceptible to the disease. The last point was elaborated in a subsequent paper by Paul.[24]

PROCEDURE

The cases studied were from Montefiore Hospital and Bellevue Hospital,[25] New York City. At Montefiore Hospital the patients were distributed in five wards and in the convalescent pavilion. Those in the pavilion were ambulatory, whereas those in the wards were for the most part confined to bed. Each ward has eighteen beds, and there are a number of smaller rooms adjoining, each containing from two to seven beds. Visitors are permitted twice a week for two hours. The possibility of contact infection exists. No cultures were made from the throats of visitors to the wards, however. In Bellevue Hospital, two children's wards were studied. Each ward is divided into nineteen cubicles and contains approximately thirty-two beds. Visiting hours are two hours twice a week.

The throat cultures included tonsillar, pharyngeal and nasopharyngeal swabs. For a time cultures were taken from two different sources.

22. Bradley, W. H.: Epidemic Acute Rheumatism in a Public School, Quart. J. Med. **1**:79, 1932.

23. Paul, John R., and Salinger, R.: The Spread of Rheumatic Fever Through Families, J. Clin. Investigation **10**:33, 1931.

24. Paul, John R.: Age Susceptibility to Familial Infection in Rheumatic Fever, J. Clin. Investigation **10**:53, 1931.

25. Dr. Charles Hendee Smith, Director of the Pediatrics Division of Bellevue Hospital, permitted us to study the cases in his service.

It was found that the nasopharyngeal swabs yielded slightly better results than the others, and this method alone was used in the later cultures. The swabs were placed in dry sterile tubes and were brought to the laboratory. At first duplicate swabs were placed in tubes of various culture mediums during their transportation, but it was found that the results were practically the same as when a dry tube was used, and this method was discontinued.

Davis,[26] in 1912, studied tonsillar cultures in a series of persons suffering from chronic articular, renal and cardiac diseases and from chronic tonsillitis. He observed that surface cultures only occasionally showed hemolytic streptococci, whereas cultures made from the crypts of extirpated tonsils revealed this organism much more frequently. Pilot and Davis,[27] in 1919, apparently confirmed this observation; they reported hemolytic streptococci in 61 per cent of swab cultures and in 97 per cent of cultures taken from the crypts of excised tonsils. These tonsils were not normal. The same authors called attention to the fact that in swab cultures of normal tonsils Ruediger[28] found hemolytic streptococci in 59 per cent and Smillie[29] in 50 per cent, and that in cultures made directly from the crypts Nichols and Bryan[30] found them in 50 per cent. They were rather loath to accept this similarity of results and attempted to explain it on the ground that it is difficult to make cultures directly from the crypts with the tonsils in situ. In 1921, Pilot and Pearlman[31] emphasized this point by reporting hemolytic streptococci in 55 per cent of nasopharyngeal swabs and swabs from the surfaces of the adenoids, whereas cultures from the excised tonsils of the same patients yielded positive results in 95 per cent.

In our study it was not possible to make cultures from the excised tonsils. When tonsillar swabs were made, the tonsil was compressed in order to force to the surface any material that might be in the crypts. We appreciate that this is not so effective as making cultures directly from the crypts in the excised tonsils. However, it seems to be of some importance to note the percentage of persons in whom hemolytic strep-

26. Davis, D. J.: Bacteriology and Pathology of the Tonsils, J. Infect. Dis. **10**:148, 1912.

27. Pilot, I., and Davis, D. J.: Hemolytic Streptococci in the Faucial Tonsil and Their Significance as Secondary Invaders, J. Infect. Dis. **24**:386, 1919.

28. Ruediger, G. F.: Streptococci from Scarlatinal and Normal Throats and from Other Sources, J. Infect. Dis. **3**:755, 1906.

29. Smillie, W. G.: Studies of the Beta Hemolytic Streptococcus, J. Infect. Dis. **20**:45, 1917.

30. Nichols, H. J., and Bryan, J. H.: The Tonsils as Foci of Infection in Streptococcus Hemolyticus Carriers, J. A. M. A. **71**:1813 (Nov. 30) 1918.

31. Pilot, I., and Pearlman, S. J.: Bacteriologic Studies of the Upper Respiratory Passages, J. Infect. Dis. **29**:47, 1921.

tococci invade the surface of the tonsils and the nasopharynx, in contradistinction to those who show them only in the deep recesses of the tonsils, which, according to the authors just quoted, seems to be the universal finding.

A streak plate and two or three dilution pour plates were made of each culture. The plates were prepared in the following manner: A swab was placed in a small amount of veal infusion broth with a p_H of from 7.6 to 7.8 and was rotated to remove organisms. The swab was then removed from the broth and was rolled over a blood veal infusion agar plate, from which a streak was subsequently made. From the veal infusion broth two or three standard blood agar pour plates were made. The original veal broth was so diluted that at least one pour plate would be likely to have a good seeding. The pour plates were made of 12 cc. of veal infusion agar with a p_H of from 7.6 to 7.8, cooled to from 40 to 42 C., and 5 per cent of horse blood plus the dilution of the organism. The pour plates were incubated aerobically for forty-eight hours; the streak plates, for from twenty-four to forty-eight hours.

In 107 cultures, or 13 per cent, duplicate agar pour plates were made with rabbit blood and horse blood to ascertain whether there was an advantage in the rabbit blood. Forty-eight cultures, or slightly less than half the total number, showed hemolytic streptococci. In 12 cultures the rabbit blood appeared to favor the development of Streptococcus haemolyticus more than the horse blood; in 7 cultures the reverse held true, while in 21 cultures the blood from the two specimens appeared to be of approximately equal value for the development of these organisms. Variations were observed in the degree of hemolysis produced in the two kinds of blood by the same cultures. Six cultures showed hemolytic streptococci in the rabbit blood agar pour plates and not in the horse blood agar pour plates, while 2 cultures showed colonies of hemolytic streptococci in the horse blood agar but not in the rabbit blood agar. Furthermore, in some cases the rabbit blood seemed better suited for the development of throat flora. In general, it would appear that rabbit blood is slightly better than horse blood; but if appropriate dilutions are made of the culture in the preparation of pour plates, the species of animal from which the blood is obtained seems to be of relatively slight importance. In arriving at this conclusion we realized that our method was one which would give at best only a rough quantitative index of hemolytic streptococci. Moreover, none of our glassware was calibrated, and slight errors in volumetric measurements would color our results. However, our aim was to develop not an exact quantitative procedure but a reliable qualitative method which would also serve as a quantitative estimate. The medium recommended by Mueller and

Whitman [32] was also tried but was not found so satisfactory as the veal infusion base.

All the plates were examined by the aid of a binocular culture microscope, and many of the hemolytic colonies were examined for more detailed characters with the low power of a compound miscroscope. The streak plate was used for rough differentiation and for the detection of various groups of organisms. The pour plate was used for the detection of Streptococcus haemolyticus. The colonies were classified as hemolytic, green-producing and indifferent. The percentage of incidence of each class, as well as the total growth per plate, was recorded. Of the colonies producing hemolysis, 3 or more specimens of each type were examined microscopically and were subcultured on blood agar plates. This procedure was followed to ascertain whether hemolytic organisms other than Streptococcus haemolyticus, such as Hemophilus haemolyticus [33] were present. To check the question of hemolysis a pour plate of one of the pure subgenerations of each type of organism was made. In addition, hemolysin tests were carried out with tubes. Hemolysis, as evidenced in the pour plates and in the tubes, checked in all but 3 cultures. These cultures have not been included in our tabulations of hemolytic streptococci.

In the latter part of our work, in addition to the regular examination of the streak and pour plates, more detailed observations of colonies and more detailed morphologic observations were made in order to determine the percentage of incidence of Hemophilus haemolyticus, diphtheroids, pneumococci and staphylococci. Ten per cent of 163 cultures yielded hemolytic organisms of the type Hemophilus haemolyticus. Eleven patients showed these organisms; all were suffering from rheumatic fever. In pour plates as well as in streak plates the colonies of Hemophilus haemolyticus could be differentiated from those of hemolytic streptococci. Whereas the deep colony of the hemolytic streptococcus in transmitted light was either biconvex, triangular or rosette-like and was large, dark, grayish white, dense, opaque and granular throughout, the deep colony of Hemophilus haemolyticus was always simple and was smaller, much lighter in appearance, almost translucent and relatively smooth, the surface only appearing somewhat granular. Diphtheroids were present in 22 per cent of 172 cultures. Eleven per cent of 131 cultures showed organisms which resembled morphologically and colonially the pneumococcus and which were soluble in bile. In 4 per cent of 181 cultures hemolytic staphylococci predominated.

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32. Mueller, J. H., and Whitman, L.: An Improved Method for the Detection of Hemolytic Streptococcus Carriers, J. Bact. **21**:219, 1931.

33. Pritchett, I. W., and Stillman, E. G.: Occurrence of Bacillus Influenzae in Throats and Saliva, J. Exper. Med. **29**:259, 1919.

RESULTS

The number of cases from Montefiore Hospital recorded in this report is 261. The total number of cultures is 727. The investigation covered parts of three years—1931, 1932 and 1933—but the greater number of cases was studied during the winter and spring of 1932. Owing to the mildness of the winter of 1931-1932 (which was the warmest in more than one hundred years, east of the Rocky Mountains, according to the United States Weather Bureau charts) and to the relatively few cases of infection of the upper respiratory tract which developed in the hospital, the investigation was continued during the winter and spring of 1932-1933. However, during this period no great number of infections of the upper respiratory tract appeared among the hospital population. During the period 1931-1932 one slight epidemic of infection of the upper respiratory tract occurred. It started on February 26, 1932, continued with little, if any, abatement through March 3 and had completely subsided by March 28. At Bellevue Hospital the number of cases and the number of cultures were 60 and 113, respectively. The period of investigation was from February 1 to May 11, 1932. No epidemics were reported in the two wards in which these patients were located. The months during which cultures were obtained from Montefiore Hospital were December, 1931, the first six months of 1932 (through June 1) and the first four months of 1933. The greatest number of cultures for any single month was taken in March, 1932. Thus the seasonal incidence of the cultures coincided with the season of the year when increases in acute attacks of rheumatic fever were found most likely to occur.

The cases from Montefiore Hospital have been grouped in five broad diagnostic divisions. Group 1 includes ward patients suffering from active or chronic rheumatic fever and is designated as the chronic rheumatic cardiovalvular disease (CRCVD) group. It includes 101 cases and 390 cultures. These cases represent 39 per cent of all cases, and the cultures represent 54 per cent of the total number of cultures. The age of the members of the group varies from 3 to over 60 years of age. Fifty-three per cent of the patients were males, and 47 per cent were females. Tonsillectomy had been performed on 61 per cent of the group.

The other four groups are control groups and include ward patients suffering from conditions unrelated to rheumatic fever (groups 2, 3 and 4) and normal persons (group 5), composed of doctors, nurses and attendants on duty at the hospital. These four groups include 160 cases and 337 cultures and represent 61 and 46 per cent of the total number of cases and cultures, respectively. Group 2 includes persons suffering from arthritis, other than that caused by acute rheumatic fever. The cases in this division represent only 2 per cent of the total number,

and the cultures represent the even smaller number of 1 per cent. Group 3, known as the group of "other cardiac conditions," is composed chiefly of cases of hypertension, arteriosclerosis, disease of the coronary arteries and subacute bacterial endocarditis (4 cases). This group comprises 81 cases (31 per cent) and 183 cultures (25 per cent). The age range is higher here than in the other groups. In Group 4 have been placed all the manifestations of disease not recorded elsewhere. It is known as the division of "other conditions." Analysis of this division shows 59 cases (23 per cent) and 129 cultures (18 per cent). The most frequent diseases are diabetes mellitus, nephritis and cirrhosis of the liver, but there are in all 32 different diseases. These include such conditions as Banti's disease, lesions of the brain, Cooley's anemia, encephalitis, exophthalmic goiter, kala-azar, pulmonary abscess, osteomyelitis, pyelitis, tuberculosis and ulcerative colitis. Group 5 includes 17 cultures taken from 14 normal persons. These constitute 5 per cent of the cases and 2 per cent of the cultures.

In the control groups 66 per cent of the subjects were males, as compared with 53 per cent in the group with chronic rheumatic cardiovalvular disease. Tonsillectomy was known to have been performed in only 27 per cent of the cases, as against 61 per cent in the rheumatic group.

Forty-seven per cent of all the subjects, or 114, had one throat culture. The remaining 46 per cent, or 67 subjects, had from 2 to 20 repeat cultures. Analysis of this 46 per cent on the basis of the individual groups shows that 68 per cent of the patients with rheumatic fever had 2 or more repeat cultures per case. By making frequent cultures from the throats of the patients who were suffering from rheumatic fever it was hoped to obtain more definite information concerning the presence of hemolytic streptococci in infections of the throat and thereby to correlate, if possible, their presence during this period with an exacerbation of the disease. The mean number of cultures per case is 2.8; for group 1 it is 3.9, and for the control groups, 2.1.

The cases and cultures from Bellevue Hospital were analyzed in the same manner. There were no cases of arthritis, but there were a number of patients with chorea. No person in any of the groups was over 14 years of age. In the group of patients with chronic rheumatic cardiovalvular disease there were 34 cases and 82 cultures. There were also 14 cases of chorea, 3 of cardiac conditions not due to rheumatic fever and 9 of other diseases. The number of cultures in each of these groups was 17, 5 and 9, respectively. Two of the 3 subjects suffering from other cardiac conditions had subacute bacterial endocarditis. Other diseases included nephritis, pemphigus, encephalitis, diabetes mellitus, pneumonia and epilepsy. Fifty-six per cent of the patients with chronic rheumatic cardiovalvular disease were males; ton-

sillectomy had been performed on 68 per cent. In the other groups, 35 per cent were males; 46 per cent had had their tonsils removed. The number of repeat cases ranged from 2 to 6, but only 4 of the controls had more than 1 culture. Among the patients with rheumatic fever 28 had repeat cultures. The mean number of cultures per case was 2.1.

For a full and perhaps more exact interpretation of the data, it seemed desirable to analyze the material in terms of subjects and the total number of throat cultures and to divide all groups into three age divisions. The following classifications were made: subjects under 15 years of age, those between 15 and 29 years and those 30 years of age and over. All the patients from Bellevue Hospital were under 15 years of age.

TABLE 1.—*Incidence of Cases and Cultures According to Age (Montefiore Hospital)*

Group	Cases			Cultures		
	14 Years and Below	15-29 Years	30 Years and Above	14 Years and Below	15-29 Years	30 Years and Above
1. Chronic rheumatic cardiovalvular disease..	41 (40%)	21 (21%)	39 (39%)	231 (59%)	79 (20%)	80 (21%)
2. Arthritis.....	0	1 (17%)	5 (83%)	0	2 (25%)	6 (75%)
3. Other cardiac conditions.....	2 (3%)	6 (7%)	73 (90%)	4 (2%)	21 (12%)	158 (86%)
4. Other conditions.....	16 (27%)	7 (12%)	36 (61%)	43 (33%)	17 (13%)	69 (54%)
5. Normal persons.....	0	13 (93%)	1 (7%)	0	16 (94%)	1 (6%)
Total.....	59 (23%)	48 (18%)	154 (59%)	278 (38%)	135 (19%)	314 (43%)

Table 1 shows the incidence of cases and cultures from Montefiore Hospital according to age. Of the 101 subjects suffering from chronic rheumatic cardiovalvular conditions, 41 (40 per cent) had active cases and were under 15 years of age; 21 (21 per cent) were between 15 and 29, and 39 (39 per cent) had chronic cases and were 30 years old or more. Of the 390 cultures, 231 (59 per cent) were taken from members of the first group, 79 (20 per cent) from members of the second group and 80 (21 per cent) from the last group. Thus there were available for study a fair number of cases of rheumatic fever in each age group. Of the total number of cases and cultures from the group of patients with rheumatism, more than one-third and one-half, respectively, fall in the group under 15 years of age. The total number of control subjects under 15 years in the four groups is slightly less than half the number in the group of subjects with rheumatic fever, and the total number of cultures equals, roughly, one-fifth the number of those in group 1. The cases and cultures in the controls between 15 and 29 years are more numerous, but no single division approximates the number in the rheumatic fever group.

In table 2 the data from Montefiore Hospital are analyzed with reference to the occurrence of hemolytic streptococci in the throat cultures and throats of the subjects. No age groups are observed; these have been left to a later analysis in which the question of correlation between infection of the upper respiratory tract and the presence of hemolytic streptococci is considered. From a study of the data, it appears that Streptococcus haemolyticus is found no more frequently in the throat cultures of persons suffering from rheumatic fever than in those of other persons. Hemolytic streptococci seem to be present in about 25 per cent of the throat cultures of the hospital population. When an analysis is made in terms of subjects rather than of the total number of cultures and a comparison is made with the former data, it is observed that as repeat cultures are taken from the same group of hospital

TABLE 2.—*Incidence of Hemolytic Streptococci in Throat Cultures and Throats (Montefiore Hospital)*

	Cases			Cultures		
		Incidence of Hemolytic Streptococci			Incidence of Hemolytic Streptococci	
Group	Total	Present	Absent	Total	Present	Absent
Chronic rheumatic cardiovalvular disease	101*	43 (43%)	57 (56%)	390*	86 (22%)	303 (77%)
Arthritis	6	0	6 (100%)	8	0	8 (100%)
Other cardiac conditions	81	31 (38%)	50 (62%)	183	52 (28%)	131 (72%)
Other conditions	59*	17 (29%)	41 (70%)	129*	29 (22%)	99 (77%)
Normal persons	14	2 (14%)	12 (86%)	17	5 (29%)	12 (71%)
Total controls	160	50 (31%)	109 (68%)	337	86 (26%)	250 (74%)
Total	261	93 (36%)	166 (64%)	727	172 (24%)	553 (76%)

* One culture showed no growth.

patients there is a tendency for positive results to increase. It appears from table 2 that the tendency is more marked in patients with rheumatic fever than in patients suffering from other diseases. The percentage of persons with rheumatic fever who give throat cultures which are positive for hemolytic streptococci is 43. The highest percentage in any control group is 38, and the total for all the control groups is 31. However, in formulating these conclusions account must be taken of the fact that the number of patients with rheumatic fever and the number of throat cultures from this group are greater than in any control group and that 68 per cent of the patients with rheumatic fever, as against less than 50 per cent of the controls, had repeat cultures. Thus the higher percentage of hemolytic streptococci in the rheumatic fever group may be merely apparent, and the percentages in the various groups might be more nearly equal if large numbers of throat cultures from nonrheumatic subjects had been taken.

The data from Bellevue Hospital (table 3) have been collected in a similar manner. The control groups are small. Because of this they

have been considered not only individually but also collectively. Just as with the material taken from Montefiore Hospital, there is a tendency for throat cultures which are positive for hemolytic streptococci to increase as repeat cultures are taken from the same group of subjects. This trend is more marked in the group from Bellevue Hospital than in that from Montefiore Hospital. These differences may be partly

TABLE 3.—*Incidence of Hemolytic Streptococci in Throat Cultures and Throats (Bellevue Hospital)*

	Cases			Cultures		
		Incidence of Hemolytic Streptococci			Incidence of Hemolytic Streptococci	
Group	Total	Present	Absent	Total	Present	Absent
Chronic rheumatic cardiovalvular disease	34	20 (59%)	14 (41%)	82	31 (38%)	51 (62%)
Chorea	14	4 (29%)	10 (71%)	17	4 (23%)	13 (77%)
Other cardiac conditions	3	0	3 (100%)	5	0	5 (100%)
Other conditions	9	6 (67%)	3 (33%)	9	6 (67%)	3 (33%)
Total rheumatic	48	24 (50%)	24 (50%)	99	35 (35%)	64 (65%)
Total nonrheumatic	12	6 (50%)	6 (50%)	14	6 (43%)	8 (57%)
Grand total	60	30 (50%)	30 (50%)	113	41 (36%)	72 (64%)

TABLE 4.—*Percentage of Incidence of Colonies of Hemolytic Streptococci in Throat Cultures (Montefiore Hospital)* *

Group	Total Number of Cultures	Cultures Showing Hemolytic Streptococci	1-10%	11-20%	21-30%	31-40%	41-50%	Above 50%
Chronic rheumatic cardiovalvular disease	390	86	51 (59%)	10 (12%)	7 (8%)	6 (7%)	2 (2%)	10 (12%)
Arthritis	8	0						
Other cardiac conditions	183	52	29 (56%)	5 (10%)	7 (13%)	7 (13%)	..	4 (8%)
Other conditions	129	29	20 (69%)	1 (3%)	2 (7%)	3 (10%)	1 (3%)	2 (7%)
Normal persons	17	5	2 (40%)	..	..	..	..	3 (60%)

* The percentages are based on the number of cultures which showed hemolytic streptococci.

accounted for by the fact that the patients from Bellevue Hospital were either children or adolescents, whereas the subjects with rheumatic fever from Montefiore Hospital included 51 adults.

The next question of interest is whether patients suffering from rheumatic fever have a greater percentage of hemolytic streptococci in their throats than do other persons. In table 4 data are given which relate to this subject. The patients from Bellevue Hospital have been omitted in this analysis, as the number of controls is too small for a basis of comparison. The cultures from each diagnostic group have

been divided into six subdivisions according as the percentages of hemolytic streptococci comprised, roughly, from 1 to 10 per cent, from 11 to 20 per cent, from 21 to 30 per cent, from 31 to 40 per cent, from 41 to 50 per cent or more than 50 per cent of the total throat flora, as ascertained by dilution pour plates. The percentages of each division have been obtained by using the total number of cultures showing hemolytic streptococci in each diagnostic group. The table shows that there is no tendency for hemolytic streptococci to occur more abundantly in the throats of patients with rheumatic fever than in those of other patients. In fact, in this study Streptococcus haemolyticus seems to occur slightly more abundantly in the throat cultures of subjects suffer-

TABLE 5.—*Incidence and Preponderance of Green-Producing and Indifferent Streptococci in Cases of Chronic Rheumatic Cardiovalvular Disease (Montefiore and Bellevue Hospitals)*

		Green-Producing Streptococci					Indifferent Streptococci				
Age, Years	Total No. of Cases	Present	Absent	Predominating*	Not Predominating	Undetermined†	Present	Absent	Predominating*	Not Predominating	Undetermined†
14 and below....	75	75 (100%)	0	51 (68%)	7 (9%)	17 (23%)	70 (93%)	5 (7%)	0	70 (93%)	5 (7%)
15 to 29.....	21	21 (100%)	0	12 (57%)	0	9 (43%)	21 (100%)	0	0	19 (90%)	2 (10%)
30 and above...	39	39 (100%)	0	30 (77%)	4 (10%)	5 (13%)	39 (100%)	0	0	37 (95%)	2 (7%)
Total.....	135	135 (100%)	0	93 (69%)	11 (8%)	31 (23%)	130 (96%)	5 (4%)	0	126 (93%)	9 (7%)

* More than 50 per cent of the total number of organisms in culture.
† In early cultures organisms were listed merely as present or absent.

ing from cardiac conditions other than chronic rheumatic cardiovalvular disease. In the normal group, in which there is a much smaller number of cases than in any of the other groups, there is a disproportionately large percentage of cultures showing over 50 per cent of hemolytic streptococci. These cultures were all taken from one person. Because of the hemolytic streptococci in her throat, more repeat cultures were taken from her than from any of the other normal controls. This accounts for the unusually high percentage. To determine whether hemolytic streptococci would appear in greater abundance in the throat flora of subjects with active rheumatic fever than in the throat flora of those with chronic cases, our data were again analyzed. The results remained essentially the same as those already recorded. For example, in 54 per cent of the cultures hemolytic streptococci constituted from 1 to 10 per cent of the flora. This contrasted with 59 per cent when

the entire group of cases of rheumatic fever was considered. In the other divisions the percentages were about the same.

Data on the incidence and preponderance of nonhemolytic streptococci in cases of rheumatic fever and in cultures are presented in tables 5 and 6. A number of cases and cultures are listed as "undetermined." This is due to the fact that at the beginning of our study green-producing and indifferent streptococci were recorded merely as present or absent. In some of the cases that were followed for a long period, cultures at one time might show a preponderance of green-producing streptococci and at another time a preponderance of indifferent streptococci. These cases were likewise listed in the "undetermined" column. Green-pro-

TABLE 6.—*Incidence and Preponderance of Green-Producing and Indifferent Streptococci in Throat Cultures of Patients with Chronic Rheumatic Cardiovalvular Disease (Montefiore and Bellevue Hospitals)*

		Green-Producing Streptococci					Indifferent Streptococci				
Age, Years	Total No. of Cultures	Present	Absent	Predominating*	Not Predominating	Undetermined†	Present	Absent	Predominating*	Not Predominating	Undetermined†
14 and below....	313	310 (99%)	3 (1%)	231 (74%)	53 (17%)	29 (9%)	268 (86%)	45 (14%)	3 (1%)	282 (90%)	28 (9%)
15 to 29.....	79	79 (100%)	0	54 (68%)	19 (24%)	6 (8%)	71 (90%)	8 (10%)	5 (6%)	63 (80%)	11 (14%)
30 and above...	80	80 (100%)	0	62 (78%)	12 (15%)	6 (7%)	78 (98%)	2 (2%)	5 (6%)	69 (86%)	6 (8%)
Total.....	472	469 (99%)	3 (1%)	347 (73%)	84 (18%)	41 (9%)	417 (88%)	55 (12%)	13 (3%)	414 (87%)	45 (10%)

* More than 50 per cent of the total number of organisms in culture.
† In early cultures organisms were listed merely as present or absent.

ducing streptococci were present in all the cases, and they predominated in 69 per cent. In 8 per cent of the cases they were not in the majority, and in 23 per cent their relative number was undetermined. Indifferent streptococci were present in 96 per cent of the cases, but they did not predominate in any. In 7 per cent the percentage of incidence was undetermined.

In tabulating the cultures, green-producing streptococci were present in 99 per cent and predominated in 73 per cent, while indifferent streptococci were present in 88 per cent and predominated in 3 per cent. In this connection it is interesting to note that Hitchcock,[34] in his studies on rheumatic and nonrheumatic patients at the hospital of the Rocke-

34. Hitchcock, C. H.: Studies on Indifferent Streptococci: Observations on Distribution of Indifferent Streptococci in Throats of Rheumatic and Non-Rheumatic Individuals, J. Exper. Med. **48**:403, 1928.

feller Institute, found that 85 per cent carried indifferent streptococci in their throats. He believed that if repeated throat cultures were taken practically every person at some time or other would be found to harbor these organisms, even though they might be present in small numbers.

Many investigators have agreed that the majority of attacks or exacerbations of rheumatic fever are preceded by sore throat or by some infection of the upper respiratory tract. We attempted to ascertain if persons who were definitely known to have rheumatic fever have hemolytic streptococci associated with infections of the upper respiratory tract more frequently than do other persons. In tables 7, 8 and 9 data from Montefiore and Bellevue Hospitals are correlated which bear on this point.

In the light of previous investigations on the rôle played by the tonsils in first attacks and exacerbations of rheumatic fever, we divided our groups into subjects whose tonsils had not been removed and subjects on whom tonsillectomy had been performed. Sixty-one per cent of the patients with rheumatic fever from Montefiore Hospital and 27 per cent of the controls had had their tonsils removed. Seventy-two per cent of the cultures from the patients with rheumatic fever and 29 per cent of those from the controls were taken from throats in which there were no tonsils.

Throat cultures which yielded hemolytic streptococci at the time of an infection of the upper respiratory tract and which continued to show these organisms after the infection had subsided are grouped as infections of the upper respiratory tract caused by hemolytic streptococci. Four relationships have been tabulated: infection of the upper respiratory tract in which hemolytic streptococci are found; infection of the upper respiratory tract in which hemolytic streptococci are not found; absence of an infection of the upper respiratory tract, with the presence of Streptococcus haemolyticus, and absence of an infection of the upper respiratory tract, with the absence of Streptococcus haemolyticus. The analyses were made on the basis of the total number of throat cultures and subjects.

Relatively few patients in any of the diagnostic groups at Montefiore Hospital suffered from infections of the upper respiratory tract, and in these cases the majority of throat cultures showed no hemolytic streptococci (table 7). Of the 70 throat cultures taken from rheumatic patients during infections of the upper respiratory tract, 26 (37 per cent) showed hemolytic streptococci, while 44 (63 per cent) did not. Eleven throat cultures (61 per cent) from patients suffering from other cardiac conditions showed Streptococcus haemolyticus associated with infection of the upper respiratory tract, while 7 (39 per cent) did not. Analyses of cultures from subjects suffering from diseases unrelated to the ones just mentioned or from normal persons showed higher per-

TABLE 7.—*Association of Infection of the Upper Respiratory Tract with Hemolytic Streptococci in Throat Cultures (Montefiore Hospital)* *

Group	Age, Years	Infection of Upper Respiratory Tract						No Infection of Upper Respiratory Tract					
		Hemolytic Streptococci Present			Hemolytic Streptococci Absent			Hemolytic Streptococci Present			Hemolytic Streptococci Absent		
		Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total
Chronic rheumatic cardiovalvular disease	1-14	2	13	15 (39%)	3	20	23 (61%)	16	26	42 (22%)	23	128	151 (78%)
	15-29	..	7	7 (41%)	2	8	10 (59%)	3	5	8 (13%)	8	46	54 (87%)
	30 +	..	3	4 (27%)†	8	3	11 (73%)	9	1	10 (15%)	32	20	54 (83%)‡‖
Total		2	23	26 (37%)	13	31	44 (63%)	28	32	60 (19%)	63	194	259 (81%)
Arthritis	1-14	..	..	.....	..	..	.....	..	..	.....	..	..	.....
	15-29	..	..	.....	..	..	.....	..	..	.....	..	2	2 (100%)
	30 +	..	..	.....	..	..	.....	..	..	.....	5	1	6 (100%)
Total		..	..	.....	..	..	.....	..	..	.....	5	3	8 (100%)
Other cardiac conditions	1-14	3	..	3 (100%)	..	..	.....	..	1	1 (100%)	..	..	.....
	15-29	..	..	.....	1	1	2 (100%)	1	..	1 (5%)	4	12	18 (95%)‡
	30 +	8	..	8 (62%)	5	..	5 (38%)	35	4	39 (27%)	82	21	106 (73%)§
Total		11	..	11 (61%)	6	1	7 (39%)	36	5	41 (25%)	86	33	124 (75%)
Other conditions	1-14	4	2	6 (86%)	..	1	1 (14%)	1	5	6 (17%)	15	15	30 (83%)
	15-29	..	..	.....	..	..	.....	..	1	1 (6%)	..	16	16 (94%)
	30 +	..	..	.....	3	1	4 (100%)	14	2	16 (25%)	37	8	48 (74%)§‖
Total		4	2	6 (55%)	3	2	5 (45%)	15	8	23 (19%)	52	39	94 (80%)
Normal persons	1-14	..	..	.....	..	..	.....	..	..	.....	..	..	.....
	15-29	4	..	4 (80%)	1	..	1 (20%)	1	..	1 (9%)	6	4	10 (91%)
	30 +	..	..	.....	..	..	.....	..	..	.....	..	1	1 (100%)
Total		4	..	4 (80%)	1	..	1 (20%)	1	..	1 (8%)	6	5	11 (92%)

* Records as to the presence of the tonsils are incomplete.
† For one culture.
‡ For two cultures.
§ For three cultures.
‖ One culture showed no growth.

TABLE 8.—*Association of Infection of the Upper Respiratory Tract with Hemolytic Streptococci in Throats (Montefiore Hospital)* *

Group	Age, Years	Infection of Upper Respiratory Tract						No Infection of Upper Respiratory Tract					
		Hemolytic Streptococci Present			Hemolytic Streptococci Absent			Hemolytic Streptococci Present			Hemolytic Streptococci Absent		
		Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total
Chronic rheumatic cardiovalvular disease	1-14	2	6	8 (36%)	2	12	14 (64%)	6	14	20 (34%)	11	28	39 (66%)
	15-29	..	3	3 (25%)	2	7	9 (75%)	2	2	4 (17%)	3	16	19 (83%)
	30 +	..	1	2 (25%)†	4	2	6 (75%)	8	2	10 (23%)	18	14	33 (77%)†
Total		2	10	13 (31%)	8	21	29 (69%)	16	18	34 (27%)	32	58	91 (73%)
Arthritis	1-14	..	..	.....	..	..	.....	..	..	.....	..	..	.....
	15-29	..	..	.....	..	..	.....	..	..	.....	..	1	1 (100%)
	30 +	..	..	.....	..	..	.....	..	..	.....	4	1	5 (100%)
Total		..	..	.....	..	..	.....	..	..	.....	4	2	6 (100%)
Other cardiac conditions	1-14	1	..	1 (100%)	..	..	.....	..	1	1 (100%)	..	..	.....
	15-29	..	..	.....	1	1	2 (100%)	1	..	1 (14%)	2	3	6 (86%)†
	30 +	3	..	3 (33%)	6	..	6 (67%)	22	3	25 (29%)	45	13	60 (71%)‡
Total		4	..	4 (25%)	7	1	8 (75%)	23	4	27 (29%)	47	16	66 (71%)
Other conditions	1-14	3	1	4 (80%)	..	1	1 (20%)	1	2	3 (18%)	6	8	14 (82%)
	15-29	..	..	.....	..	..	.....	..	1	1 (13%)	..	7	7 (87%)
	30 +	..	..	.....	3	..	3 (100%)	8	2	10 (25%)	23	4	30 (75%)§
Total		3	1	4 (50%)	3	1	4 (50%)	9	5	14 (22%)	29	19	51 (78%)
Normal persons	1-14	..	..	.....	..	..	.....	..	..	.....	..	..	.....
	15-29	1	..	1 (50%)	1	..	1 (50%)	1	..	1 (9%)	6	4	10 (91%)
	30 +	..	..	.....	..	..	.....	..	..	.....	..	1	1 (100%)
Total		1	..	1 (50%)	1	..	1 (50%)	1	..	1 (8%)	6	5	11 (92%)

* Records as to the presence of the tonsils are incomplete.
† For one case.
‡ For two cases.
§ For three cases.

TABLE 9.—*Association of Infection of the Upper Respiratory Tract with Hemolytic Streptococci (Bellevue Hospital)* *

Age, Years	Group	Infection of Upper Respiratory Tract						No Infection of Upper Respiratory Tract					
		Hemolytic Streptococci Present			Hemolytic Streptococci Absent			Hemolytic Streptococci Present			Hemolytic Streptococci Absent		
		Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total
						CASES							
1 to 14	Chronic rheumatic cardiovalvular disease.....	5	4	9 (31%)	1	3	4 (69%)	5	7	12 (33%)	8	16	24 (67%)
	Chorea.....	..	..	.....	..	..	.....	3	1	4 (29%)	2	8	10 (71%)
	Other cardiac conditions	..	..	.....	..	..	.....	..	..	.....	1	2	3 (100%)
	Other conditions.....	3	..	3 (75%)	..	1	1 (25%)	3	..	3 (60%)	1	..	2 (40%)†
	Total.....	8	4	12 (71%)	1	4	5 (29%)	11	8	19 (33%)	12	26	39 (67%)
						CULTURES							
1 to 14	Chronic rheumatic cardiovalvular disease.....	9	6	15 (79%)	1	3	4 (21%)	5	11	16 (25%)	11	36	47 (75%)
	Chorea.....	..	..	.....	..	..	.....	3	1	4 (24%)	2	11	13 (76%)
	Other cardiac conditions	..	..	.....	..	..	.....	..	..	.....	1	4	5 (100%)
	Other conditions.....	3	..	3 (75%)	..	1	1 (25%)	3	..	3 (60%)	1	..	2 (40%)†
	Total.....	12	6	18 (78%)	1	4	5 (22%)	11	12	23 (26%)	15	51	67 (74%)

* Records as to the presence of the tonsils are incomplete.

† For one culture.

centages than those of the rheumatic fever group. From tables 7 and 8 it appears that the younger subjects (those below 15 years and those between 15 and 29 years) had hemolytic streptococcic infections of the throat more frequently than did those above the age of 30. Thirty-six per cent of the rheumatic patients between 1 and 14 years of age, 25 per cent between 15 and 29 and 25 per cent above 30 gave cultures which were positive for hemolytic streptococci during an infection of the upper respiratory tract. Approximately the same percentage of cases was found in the group from Bellevue Hospital. Here all the patients were under 15 years of age, and 31 per cent of them gave hemolytic streptococcus cultures at the time they had an infection of the upper respiratory tract. The percentage of positive throat cultures in these two groups, however, showed wide variance. In the group from Montefiore Hospital it was 39 per cent, whereas in the group from Bellevue Hospital it was 79 per cent. It may be that these differences in the percentages are partly accounted for by the disproportion of tonsillectomies in these two institutions. Many more of the patients in Montefiore Hospital had had their tonsils removed. Among the patients with rheumatic fever at Montefiore Hospital below the age of 15 who had not had their tonsils removed, 18 out of 44 (41 per cent) gave cultures that showed hemolytic streptococci, whereas among those who had no tonsils only 39 of a total of 187 (21 per cent) gave positive cultures. The fact that the tonsils were present in the majority of controls may also be a factor in accounting for the high percentages among these groups.

Analyses of the data during periods when there were no involvements of the upper respiratory tract show that hemolytic streptococci were absent in the majority of throat cultures (table 7). It is impossible to observe any tendency for them to be found with greater frequency in the throat cultures of patients with rheumatic fever than in those of other persons. As in the case of those suffering from infection of the upper respiratory tract (table 8), hemolytic streptococci were found more frequently in the throats of the younger subjects.

We now arrive at the final question: Is there a definite relationship between exacerbations of rheumatic fever and previous infections of the upper respiratory tract with Streptococcus haemolyticus? Table 10 summarizes the findings.

The number of patients with rheumatic fever at Montefiore Hospital considered in this report is 101, but only 96 are included in the present analysis, as the data for 5 patients are too indefinite to be tabulated. Thirty patients had only 1 throat culture, but 29 of these suffered no relapse during the investigation. For 9 patients more than one relationship is recorded. In determining whether a recrudescence occurred in a patient, the following clinical symptoms were considered: rise in

temperature, marked increase in pulse rate, electrocardiographic changes, and the appearance of rheumatic nodules, purpura, polyarthritis or chorea.

Thirty-seven patients had exacerbations. Of this number, 18 suffered from an infection of the upper respiratory tract about fifteen to twenty-one days prior to a recrudescence of the rheumatic symptoms, while 19 had no recognizable inflammatory condition of the throat. It appears that exacerbations occur as frequently when there has been no infection of the throat as when one has been present. However, of the 37 patients who experienced recrudescences, 23 (62 per cent) showed throat cultures which were positive for hemolytic streptococci some three weeks or more prior to the relapse; 14 (38 per cent) had

TABLE 10.—*Relation of Infection of Upper Respiratory Tract and Hemolytic Streptococcic Infection to Exacerbations in Patients with Rheumatic Fever*

	Hemolytic Streptococci		No Hemolytic Streptococci		Total	
	Exacerbations	No Exacerbations	Exacerbations	No Exacerbations	Exacerbations	No Exacerbations
Montefiore Hospital						
Infection of upper respiratory tract	9	10	9	13	18	23
No infection of upper respiratory tract	14	11	5	41	19	52
Total	23	21	14	54	37	75
Bellevue Hospital						
Infection of upper respiratory tract	2	3	1	0	3	3
No infection of upper respiratory tract	7	3	4	8	11	11
Total	9	6	5	8	14	14

no known occurrence of these organisms, although 9 patients did experience an infection of the upper respiratory tract. Whether the 9 subjects who had an infection of the upper respiratory tract in which Streptococcus haemolyticus was not the causative agent would have shown these organisms had more cultures been taken at the time of the infection is an open question. All throat cultures were secured within from twenty-four hours to five days after the onset of the infection. Coburn and Pauli [3] noticed that Streptococcus haemolyticus usually disappeared from the throat flora within two weeks. If this organism had been the causative agent of these infections it is probable that the cultures would have yielded it, even though its proportion to the total throat flora might have been greatly reduced. There is still another factor to be borne in mind. A great number of these patients were children, and it is not unlikely that some of them had mild colds which caused very few symptoms and which were either not observed

or not recorded. Five of the patients who had exacerbations showed neither an infection of the upper respiratory tract nor a throat culture which was positive for the hemolytic streptococcus preceding the attack. Thus it is seen that of the 37 patients who suffered exacerbations of symptoms, 32 had a definite history of either an infection of the upper respiratory tract or the presence of hemolytic streptococci or both, preceding the attack.

Seventy-five patients were free from recrudescence. In 54 (72 per cent), hemolytic streptococci did not constitute a part of the throat flora during any of the periods when cultures were taken. The majority of these (41 patients) did not experience an acute condition of the upper respiratory tract. However, 21 subjects (28 per cent) did have throat cultures which were positive for the hemolytic streptococcus without any following exacerbation. But this number is small in comparison with the number who had exacerbations following Streptococcus haemolyticus infections.

In about two thirds of the patients with rheumatic fever the exacerbations of symptoms were associated with previous Streptococcus haemolyticus infections, and, roughly, the same proportion of the patients who had no exacerbations did not have this organism in their throat cultures, but for the remaining one-third in each group there is a contradictory and as yet undetermined relationship. The data from Bellevue Hospital substantiate these findings. On the whole, these results apparently confirm those of Coburn and Pauli and of other investigators who believed that there is a definite relationship between the presence of Streptococcus haemolyticus in the upper respiratory tract and an exacerbation of rheumatic symptoms within from fifteen to twenty-one days later.

SUMMARY AND CONCLUSIONS

The present investigation includes 321 cases and 840 cultures from Montefiore and Bellevue Hospitals, New York City. Forty-six per cent of the subjects were patients with rheumatic fever. Fifty-eight per cent of the cultures were taken from this group. The remainder were taken from normal persons and from patients suffering from diseases other than rheumatic fever; these constituted the control group. In more than one third of the cases of rheumatic fever and in more than one half of the cultures taken from this group the patients were under 15 years of age.

1. In making cultures of hemolytic streptococci, it seems that rabbit blood is slightly better than horse blood. However, if appropriate dilutions are made, equally good results can be obtained with horse blood.

2. The percentage of cultures which were positive for the hemolytic streptococcus taken from the throats of patients with rheumatic fever was approximately the same as that found in other persons.

3. In these positive cultures, the hemolytic streptococcus appeared to be no more abundant in those obtained from patients with rheumatic fever than in those from other persons.

4. Throat cultures of patients with rheumatic fever taken during an infection of the upper respiratory tract showed no greater incidence of hemolytic streptococci than those from other persons who were suffering from a cold or from sore throat.

5. Infections of the upper respiratory tract were found associated with Streptococcus haemolyticus more frequently in young persons who were suffering from rheumatic fever than in older patients with this disease.

6. Hemolytic streptococci were found more frequently associated with infection of the upper respiratory tract in rheumatic persons who had not had their tonsils removed than in those on whom tonsillectomy had been performed.

7. Green-producing streptococci were present in all the cases and in 99 per cent of the cultures. They predominated in 69 per cent of the cases and in 73 per cent of the cultures.

8. Indifferent streptococci were present in 96 per cent of the cases and in 88 per cent of the cultures. They predominated in 3 per cent of the cultures.

9. In the groups studied, exacerbations of acute rheumatic fever occurred as frequently when there was no infection of the throat as when there was.

10. The fact that the majority of those in whom exacerbations of rheumatic fever occurred were persons who had hemolytic streptococci in their throats suggests a possible relationship between this organism and the reappearance of the symptoms.

Dr. B. B. Oppenheimer, Director of the Medical Service, Montefiore Hospital, and Dr. W. H. Park, Director of the Bacteriologic Laboratories of New York University and Bellevue Hospital Medical College, offered helpful suggestions in the course of this work.

Book Reviews

Chronic Nephritis and Lead Poisoning. By L. J. Jarvis Nye, M.B., Ch.M. Cloth. Price, 12 shillings, six pence. Pp. 145. Sydney, Australia: Angus & Robertson, Ltd., 1933.

This interesting monograph is based on the author's careful etiologic study of a type of chronic nephritis occurring among the children and young adults of Queensland, the prevalence of which is out of proportion to that observed in the other states of Australia.

The work is a distinct addition to the present knowledge of plumbism in that it establishes a definite relationship between the constant ingestion of lead and the well known signs of intoxication and late sequelae in the form of a chronic vascular type of Bright's disease. Nye shows logically that the usual known causes of chronic nephritis do not operate in the tropical climate of Queensland; streptococcic infections are relatively rare. On the other hand, he establishes a convincing association with lead poisoning acquired earlier in a large proportion of the cases cited. Lead paint, altered to scaly or powdery forms of the carbonate as the result of exposure to the tropical sun, is shown to be the essential source. Careful investigation into the early lives of the children studied brought out important facts in regard to most of them. They lived in the common type of frame house with wide verandas which showed disintegrating paint. Some were in the habit of licking the rain-drops from the railings of the veranda, and nearly all were either thumb-suckers or nail-biters or both. Since they lived out of doors much of the time, their hands were frequently contaminated, and absorption was by the gastro-intestinal route.

The criteria for the diagnosis of plumbism are satisfactory, and the subject matter is well arranged. Several chapters are of special interest, particularly those on the source of lead and on the relationship of lead poisoning to renal disease. Unfortunately, the pathologic pesentation which the reader looks forward to is wanting, and the interest which the careful etiologic study has aroused is left suspended because of the lack of pathologic data. Perhaps more will be written on this phase of the subject later. The clinical descriptions and records of cases are good, but the correlation of the various manifestations appears to have been difficult, as it frequently is in Bright's disease.

Interest is naturally revived in speculation as to the possible etiologic relationship of lead to some of the severe types of vascular hypertension and nephritis seen in younger persons in the United States and elsewhere.

A Text-Book of Medicine. By 141 American authors. Edited by Russell L. Cecil, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital, New York City, and Foster Kennedy, M.D., F.R.S.E., Associate Editor, Diseases of the Nervous System; Professor of Neurology, Cornell University Medical College; Director, Department of Neurology, Bellevue Hospital, New York City. Third edition, revised and entirely reset. Cloth. Price, $9. Pp. 1,664, with 14 illustrations. Philadelphia: W. B. Saunders Company, 1933.

It seems obvious that the question confronting the writer of a textbook of medicine is not what shall be included in the work but what shall be left out. This work covers the field of medicine about as well as it is possible to do in a single volume. Indeed, no little ingenuity is required to compress so much information into a single book, and the editor is to be congratulated on his success in the undertaking.

Dr. Cecil states in his prefatory remarks that the task of writing a textbook of medicine today could not be satisfactorily accomplished by a single author. One

wonders if this statement might not be argued. There is a certain smoothness of style in a book by a single author that is necessarily absent when a multiplicity of authors is at work. Perhaps, however, the medical student of today has a more agile mind than his predecessor. So far as information is concerned, it is difficult to imagine a more informative book than some of the works of the past by single authors.

After all, each important subject in a textbook of medicine must be considered as an abstract of material from which an additional textbook might be written. There is reason to suspect, at least, that a more suitable abstract might be written by a man with broad general knowledge and experience than by the expert whose knowledge is more or less limited to a single field.

Whatever the opinion on single or multiple authorship, the student and practitioner will find the present work equal to any reasonable demand made on it. It is without a superior in its field today.

Klassifikation der Schizomyceten (Bakterien): Versuch einer wissenschaftlichen Klassifikation der Bakterien auf botanischer Grundlage. By Prof. Dr. Ernst Pribram. Price, 8 marks. Pp. 142. Vienna: Franz Deuticke, 1933.

The appearance of this work emphasizes the fact that a suitable and more or less satisfactory classification of bacteria is still lacking.

Pribram attempts to classify bacteria on a scientific basis, as in botany. He also attempts to apply the nomenclature of an international codex of botanic nomenclature, with the view to its practical application. This new classification and nomenclature, he hopes, will facilitate the study of bacteria and will also prove to be more practical than the system now in use. Study of the work shows what labor and time he has expended; this can be appreciated only by a scholar who has the time and interest to read the book.

With due respect to Pribram's wide experience and knowledge, which in themselves guarantee the value of the work, there are certain points that may invite some criticism, which he has foreseen. In the attempt to simplify the classification of bacteria portions have been overdone. Sometimes the important characteristics of bacteria are overlooked. One example is the grouping of Pasteurella, Brucella, Hemophilus and Neisseria in the same family.

The scientific nomenclature of Pribram's work is overshadowed by a liberal use of proper names, particularly the name of the author. It is questionable, at least among the majority of bacteriologists, whether the mere renaming of a genus, family or other class should be accompanied by the author's name.

As is stated by Pribram, the work is an outgrowth of a classification of Kral's bacteriologic collection (which at present is owned by Pribram). It may serve well as a descriptive catalog for the collection, but it is not a suitable book for laboratories or schools.

Tratado de la diabetes. By Professor Pedro Escudero. Second edition. Price, $15. Pp. 1,001. Buenos Aires: El Ateneo, 1933.

What Joslin's treatise is to English-speaking physicians Escudero's is to the Spanish, that is, a standard authoritative guide for the treatment of diabetes. The second edition is practically a new work; according to the author, there is not a page that has not been revised or modified. This revision, he points out somewhat platitudinously, was necessitated by the fact that the majority of concepts have been modified, clarified or proved, that medicine is a science in constant evolution, and that what appeared obvious yesterday is erroneous today, the impossible of other days becoming axiomatic.

The creation of the Municipal Institute of Diseases of Nutrition has made it possible for the author and his co-workers to study thousands of new cases of diabetes within the past five years. This opportunity has been tremendously important, because "the study of diabetes is the small and brilliant spot in the

firmament of diseases of nutrition and it has succeeded in orienting the study of all the nutritional diseases." Constant investigation has been in progress at the institute, and the following investigators have made many valuable contributions: Schultz Ortiz, Boscq, Orosco, Peco, Gravano, Ferradas, Casanegra, Landabure, Puchulu, Secco, Miranda Gallino, Izzo, Pangaro, Silvestri, Tobias and Silvestri.

"This book," he states in the preface, "is not a synthesis of foreign ideas filtered through our experience; it is the embodiment of doctrine, supported by the men who form our school and who look for its constant betterment by unending and honest investigation."

Handbook of Chemotherapy. Part I: Metal-Free Organic Compounds. By Dr. Viktor Fischl and Dr. Hans Schlossberger. Translated from the German by D. A. S. Schwartzman. Price, $8. Baltimore: H. G. Roebuck & Son, 1933.

This handbook represents the collaboration of a chemist and a physician. It contains therefore, detailed accounts of the chemistry of therapeutic preparations with which it deals and the opinions of the physician on the clinical results of their use. This volume is devoted to metal-free organic compounds. These are divided into eleven groups: acyclic chlorine compounds; unsaturated fatty acids; simple derivatives of benzene and naphthalene, oxy and oxo compounds; amino-acids; derivatives of quinoline (with the exception of quinine) and similar substances; quinine and its derivatives; emetine and its derivatives; the other plant substances; derivatives of acridine; the other dyestuffs, and colorless derivatives of urea.

In the discussion of such recognized chemotherapeutic agents as quinine and chaulmoogra oil, a splendid historical account of their early empirical use is given, with a satisfactory discussion of their method of action, presented in an unprejudiced manner. The same method of approach is employed in presenting the other agents. Each chapter has a complete bibliography. The volume is well translated, and the subject matter is presented clearly and concisely. This book has a place in medical literature, as it contains a large amount of information which is ordinarily not readily accessible.

Traité de physiologie normale et pathologique: Tome I: Physiologie générale. Published under the direction of G. H. Roger and Léon Binet. Price, 165 francs. Pp. 1,136, with 95 illustrations. Paris: Masson & Cie, 1933.

Although this is the first volume of an extensive work which began to appear in 1927, it is among the last volumes to be finished; all but one of the eleven volumes are off the press, and the preparation of a second edition of volumes VII and XI is announced. Each volume is complete in itself and deals with a definite division of normal and pathologic physiology. The editors have had the aid of a large number of collaborators, and the subdivisions of the subject matter of each volume are treated by various authors. This volume of 1,136 pages, the largest so far issued, deals with the following topics: the general properties of living matter, general cellular physiology, tissue culture, physical chemistry of the cells, cellular constitution, the action of physical agents (pressure, radiant energy and electricity), the action of roentgen rays and of radioactive substances, toxins, ferments and venoms. The book is essentially one of reference, the main facts of physiology being given together with much of the recent literature. It would seem to be of value chiefly to French scientists.

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